Brønsted Acid-Based Strategies for *N*–Heterocyclic Synthesis

by Stuart Adam Henry

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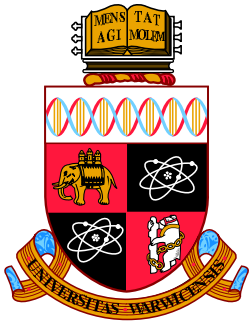

For Marie Allison Henry

1958–2006

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Declaration

I hereby declare that this thesis is my own work. To the best of my knowledge and belief it contains neither material previously published, or written by, another person, nor material which has been accepted for the award of any other degree or diploma at a university or institute of higher education, except where due acknowledgement is made in the text.

The work presented in this thesis was carried out at the Department of Chemistry, University of Warwick between October 2015 and April 2019 under the supervision of Professor Philip Wai Hong Chan.

Published journal articles based on the works presented in this thesis:

Day, D. P.; Henry, S. A.; Zhao, Y.; Jin, J.; Clarkson, G. J.; Chan, P. W. H. *Aust. J. Chem.* **2018**, *71*, 673. doi.org/10.1071/CH18191

Zhao, Y.; Henry, S. A.; Clarkson, G. J.; Chan, P. W. H. *Asian J. Org. Chem.* **2019**, *8*, 1029. doi.org/10.1002/ajoc.201900277

Abstract

The focal point of this work has been the development of new and expedient Brønsted acid–catalysed synthetic methods with alcohol pro–electrophiles to rapidly achieve molecular complexity.

Chapter 1 provides insight into notable developments within the field of Brønsted acid–mediated transformations of alcohols as pro–electrophiles.

Chapter 2 describes our efforts towards the realisation of a chiral Brønsted acid–catalysed enantioselective 1,3–allylic alcohol isomerisation of 3–indolinols.

Chapter 3 describes the synthesis of 1,2–dihydroquinolines *via* a Brønsted acid–catalysed intramolecular allylic amination.

Chapter 4 is an account of the Brønsted acid–catalysed cyclisation of *β*–amino–1,4–enols to oxazol–2(3*H*)–ones and 5–alkenyloxazolidin–2–ones.

Chapter 5 provides a summary of the works presented herein.

Chapter 6 details the experimental data and methods used in the work presented in this thesis.

Abbreviations

AAI	Allylic alcohol isomerisation
ACDC	Asymmetric counteranion–directed catalysis
BA	Brønsted acid
BINBAM	1,1′–Binaphthyl–2,2′–bis(sulphon)amide
BINOL	1,1'–Bi–2–naphthol
BINSA	1,1′–Binaphthyl 2,2′–disulphonic acid
Boc	*t*–Butoxycarbonyl
CBA	Chiral Brønsted acid
COSY	Correlated spectroscopy
CPA	Chiral phosphoric acid
CPME	Cyclopentyl methyl ether
DCE	1,2–Dichloroethane
DCM	Dichloromethane
DIPA	Diisopropylamine
dr	Diastereomeric ratio
ee	Enantiomeric excess
ESI	Electron spray ionisation
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single–quantum correlation spectroscopy
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
MS	Molecular sieves
NMR	Nuclear magnetic resonance
nr	No reaction
o–QM	*ortho*–Quinone methide
p–QM	*para*–Quinone methide
Petrol	Petroleum ether (T_b 40–60 °C)
ppm	Parts per million
rcsm	Recovered starting material
rr	Regioisomeric ratio
RT	Room temperature
SPINOL	1,1′-Spirobiindane-7,7′-diol
TBD	Triazabicyclodecene
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TRIP	2,4,6–Triisopropylphenyl
TS	Transition state
VANOL	3,3′–Diphenyl–2,2′–bi(1–naphthol)
VAPOL	2,2–Diphenyl–(4–biphenanthrol)

Chapter 1

1.0 Introduction

1.1 Chiral Brønsted Acid Catalysis

The design of efficient synthetic protocols for the construction of chiral organic compounds with a high degree of enantiopurity is, and continues to be, an actively pursued area of exploration in contemporary organic chemistry. One synthetic strategy to induce product chirality in recent years is chiral organocatalysis, a method employing a small chiral compound as the reaction catalyst. As a result of their extensive chiral pool, low cost, and lack of toxicity, in addition to their resilience to air and moisture, this field has received considerable attention from both industry and academia towards highly enantioselective transformations.[1–17]

Asymmetric Brønsted acids, in particular BINOL–based scaffolds, have been investigated extensively in the field of organocatalysis (Figure 1.1).[18] The chiral induction obtained in these reactions relies heavily on the intimate active site of the C_2–symmetry of the BINOL backbone. Further to this is the ability of the chiral pocket to remain intact as the acidic proton migrates during the mediation of a transformation.

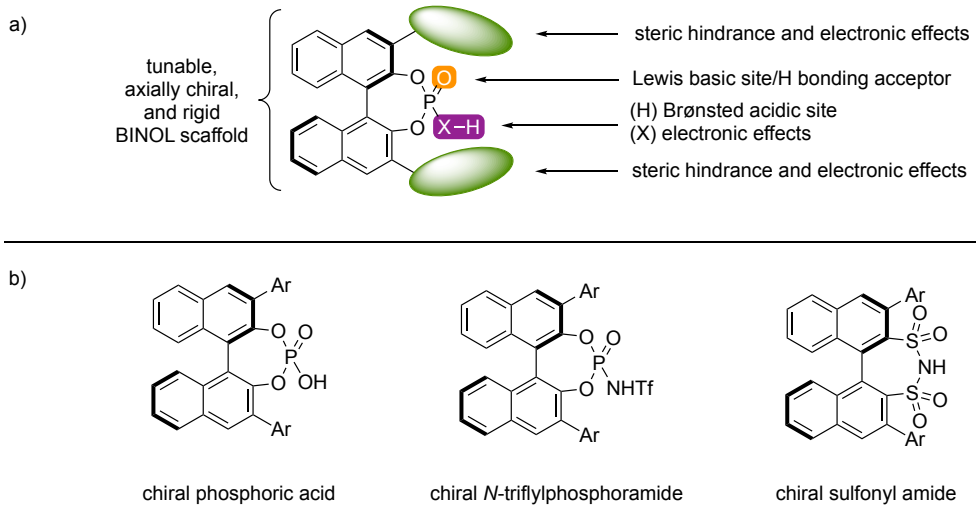


Figure 1.1: (a) Generic architecture of BINOL–based asymmetric Brønsted acid catalysts. (b) Select BINOL–based chiral Brønsted acid catalysts.

Since their inception, the development of these catalysts has been continuously pursued. For example, the imidodiphosphoric acids were developed by List *et al.* to have a more sterically demanding active site with a view to enhanced enantiofacial discrimination towards substrates lacking spatially defined interactions (Figure 1.2).[19]

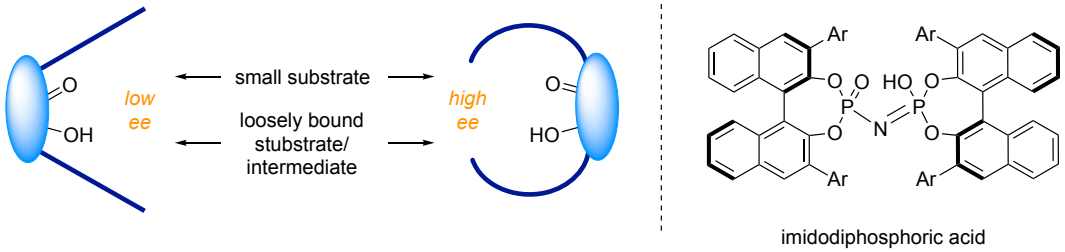


Figure 1.2: BINOL–based imidodiphosphoric Brønsted acid catalyst developed by List *et al.*

Both the (*R)* and (*S)* enantiomers of the BINOL–derived catalysts are commercially available or readily accessible *via* established synthetic procedures. This provides the ability to tailor the axially chiral backbone, with regards to both electronic properties and steric hindrance, to afford novel chiral Brønsted acids.

The classical modes of action for transformations mediated by these Brønsted acids is through interactions with a pro–electrophile, either by protonation or H–bonding. In so doing, the energy of the LUMO is lowered to generate an 'activated' substrate. The capacity in which this catalyst–substrate interaction takes place can be defined by one of four modes of function; mono–, dual–, bifunctional–, or counteranion–activation (Figure 1.3).[20] Mono–activation takes place when the substrate singularly takes part in either H–bonding or forms an ion pair with the Brønsted acid catalyst (Figure 1.3a). Dual–activation is defined by the reaction substrate making two distinct points of contact with the Brønsted acid catalyst (Figure 1.3b). The term bifunctional–activation involves a mechanism in which both an electrophilic substrate and a separate reaction nucleophile simultaneously partake in H–bonding to the acid catalyst (Figure 1.3c).

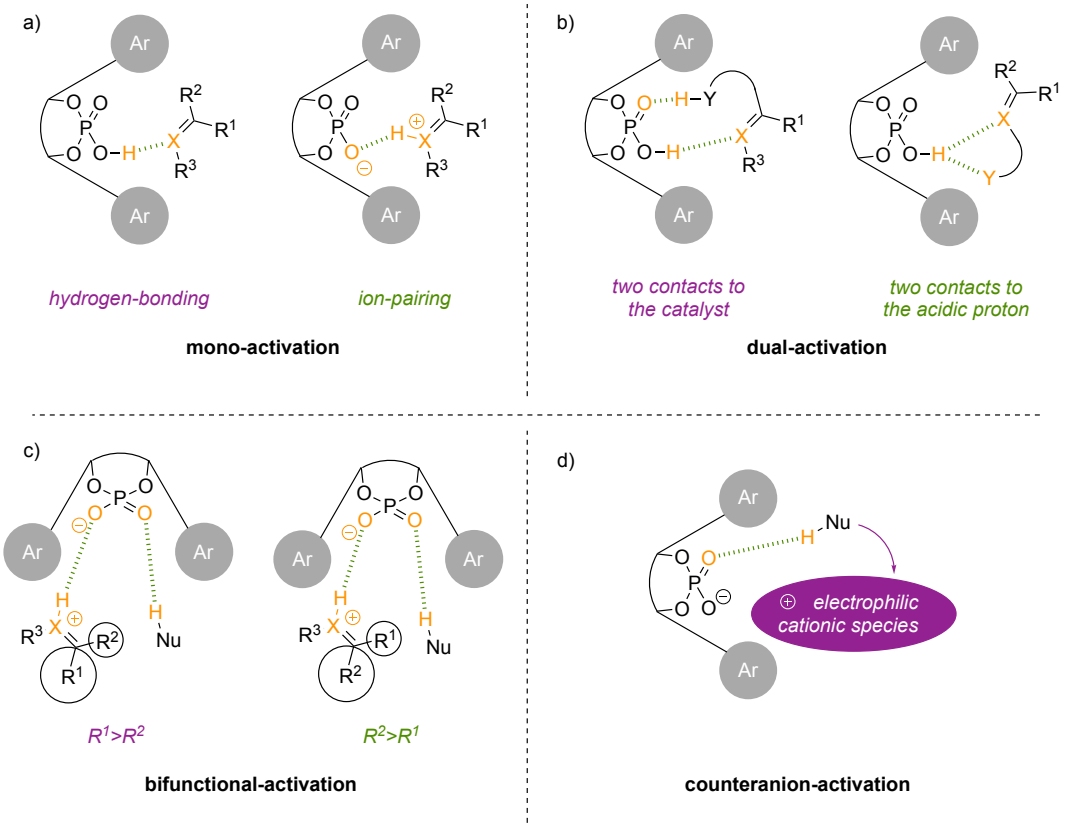


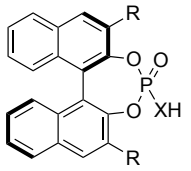
Figure 1.3: Modes of activation of chiral phosphoric acid catalysts.

This mode of action is most often proposed and investigated in chiral phosphoric acid catalysis.[21,22] Lastly, counteranion–activation, better known as asymmetric counteranion–directed catalysis (ACDC), a term coined by List *et al.,* is described as the contact ion–pairing between a cationic substrate and a chiral phosphate anion (Figure 1.3d).[23]

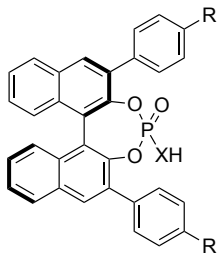
As a consequence of the versatility of these catalysts, their application to asymmetric transformations of a myriad of substrate classes that include imines, aziridines, epoxides, alcohols, and carbonyl compounds have been readily realised.[24–29] This proficiency has enabled access to a plethora of enantiopure, synthetically valuable compounds, which could not easily be accomplished previously.[30]

The focus of this Introduction is on the development of chiral Brønsted acid–mediated functional group transformations of alcohols as pro–electrophiles. In view of the

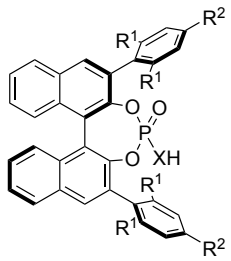
plethora of works in this area of catalysis research, only examples that best exemplify the progress made in the field have been selected to clarify the concept. Illustrated in Figure 1.4 are the acid catalysts employed in the selected synthetic studies described in this Introduction and research work of the thesis.



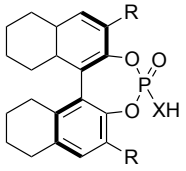
BA1, X = O, R = H
BA2, X = O, R = $SiPh_3$
BA3, X = O, R = 1-naphthyl
BA4, X = O, R = 9-anthracenyl[65,78,98]
BA5, X = O, R = 2-pyrenyl
BA6, X = O, R = 9-phenanthracenyl[80,83]
BA7, X = O, R = 2,3,4,5,6-(pentamethyl)phenyl[64,96]
BA8, X = O, R = 2-naphthyl[77]
BA9, X = O, R = 3,5-(trifluoromethyl)phenyl
BA10, X = NTf, R = 1-naphthyl
BA11, X = NTf, R = CH-diphenyl[44]
BA12, X = NTf, R = 9-anthracenyl
BA13, X = NTf, R = 2-pyrenyl



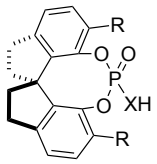
BA14, X = O, R = H
BA15, X = O, R = *t*-Bu
BA16, X = O, R = NO_2[31]
BA17, X = O, R = Ph
BA18, X = O, R = 2-naphthyl[33]
BA19, X = O, R = OMe[76]
BA20, X = O, R = Cl[79,85]
BA21, X = NTf, R = Ph[46]
BA22, X = NTf, R = *t*-Bu
BA23, X = NTf, R = H



BA24, X = O, R^1 = R^2 = *i*–Pr[43,59,97]
BA25, X = O, R^1 = Me, R^2 = *t*-Bu[52,57]
BA26, X = O, R^1 = R^2 = cyclohexyl[49]
BA27, X = NTf, R^1 = R^2 = *i*–Pr[68,69]



BA28, X = O, R = 9-phenanthracenyl[72,82,84,86]
BA29, X = O, R = 2,4,6-(triisopropyl)phenyl[60,74]
BA30, X = O, R = 1-naphthyl[72,81]
BA31, X = O, R = Ph[73]
BA32, X = O, R = 9-anthracenyl[55]
BA33, X = O, R = 2,4,6-(trimethyl)phenyl
BA43, X = NTf, R = 1-naphthyl[66]
BA44, X = NTf, R = 2,4,6-(triisopropyl)phenyl[87]
BA34, X = NTf, R = Ph[42,45]
BA35, X = NTf, R = 9-phenanthracenyl

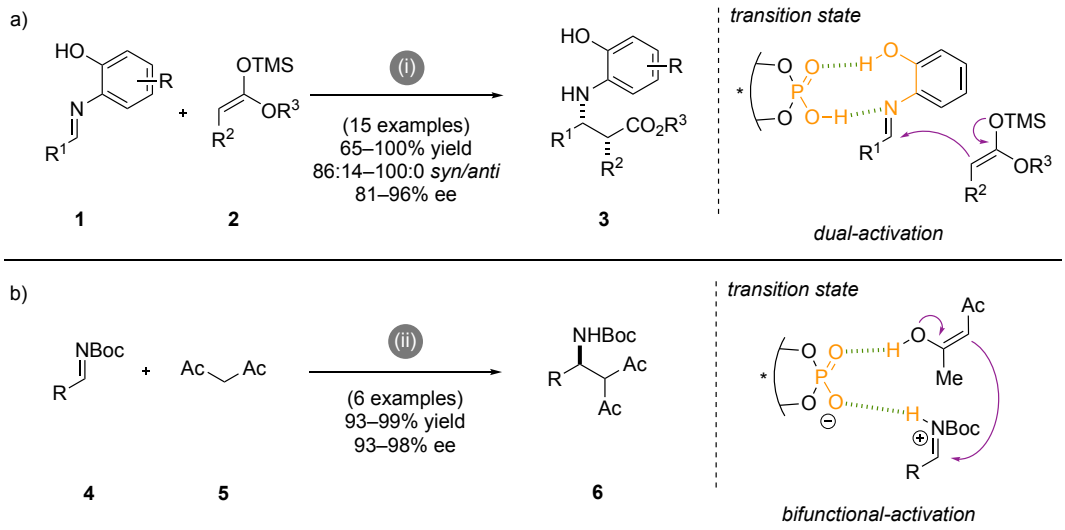


BA36, X = O, R = 9-phenanthracenyl[56,58]
BA37, X = O, R = 9-pyrenyl
BA38, X = O, R = 9-anthracenyl[54,61,62]
BA39, X = O, R = 1-pyrenyl[63,88]
BA40, X = O, R = 1-naphthyl[47]
BA41, X = O, R = 2-naphthyl[75]
BA45, X = O, R = 2,4,6-(triisopropyl)phenyl[70]
BA42, X = NTf, R = 2,4,6-(triisopropyl)phenyl[99]

Figure 1.4: Asymmetric Brønsted acid catalysts employed in the reactions discussed heretofore.

1.2 Alcohols as Pro–Electrophiles in Chiral Brønsted Acid Catalysis

Pioneering works in the area of chiral Brønsted acid catalysis were realised in 2004 by the Akiyama and Terada groups who, independently, realised the asymmetric Mannich-type reactions shown in Scheme 1.1.[31–33] In studies by Akiyama and co–

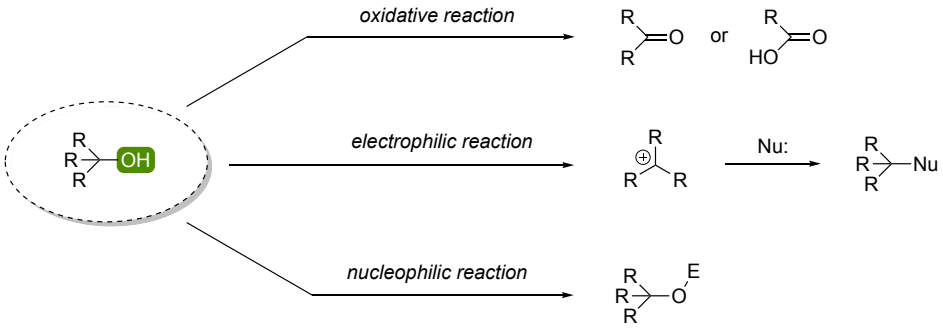


Scheme 1.1: (a) Asymmetric Mannich–type reaction of imine **1** with silyl ether **2** by Akiyama *et al.*, i) **BA16** (10 mol%), toluene, –78 °C, 24 h. (b) Asymmetric direct Mannich reaction of imine **4** with 1,3–dicarbonyl **5** by Terada and co–workers. ii) **BA18** (2 mol%), **5** (1.1 eq), DCM, RT, 1 h.

workers, the chiral phosphoric acid-catalysed reactions of imine **1** together with silyl enol ether **2** was found to furnish the corresponding enantioenriched amine adduct **3** in 65–100% yield and with 81–96% ee (Scheme 1.1a). The Terada group reported the enantioselective reaction between Boc–protected–imines **4** and 1,3–dicarbonyl compounds **5** to afford the corresponding enantiopure amines **6** in 93–99% yield and with 93–98% ee (Scheme 1.1b). In the wake of this ground-breaking research, innumerable reports have described the use of BINOL-based chiral phosphoric acids as catalysts for a broad scope of asymmetric transformations.[20] Included in this have been methods that target the enantioselective formation of products of synthetic value from alcohol pro–electrophiles.

As alcohols are ubiquitous in nature, the compound class is often viewed as ideal reagents for the development of synthetic reactions. This is in addition to their ease of synthesis and the potential for the production of water as potentially the only by–product.[34,35] Alcohols also possess the potential to participate in H–bonding interactions with the Brønsted acid catalyst, making them invaluable substrates for

asymmetric reaction development.[36,37] The functional group can exhibit the following reactivities: a) in oxidations to afford the corresponding aldehyde, ketone, or carboxylic acid; b) as the electrophile in nucleophilic substitution reactions, resulting in the loss of the hydroxyl motif, and c) as a nucleophile when the hydroxyl group attacks an electrophilic species (Scheme 1.2).



Scheme 1.2: Potential Brønsted acid–catalysed reactivities of alcohols.

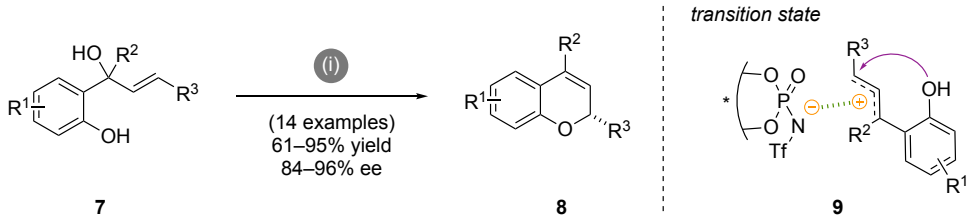
The majority of reports exploring the transformations of alcohols in chiral Brønsted acid catalysis have focused on their nucleophilic nature. In comparison, alcohols as electrophiles have received relatively limited attention. This has been viewed as a more challenging due to the intrinsically poor asymmetric environment afforded by the carbocationic species created *via* dehydration of the alcohol. As a consequence, this results in low levels of stereoinduction as the asymmetric catalyst mediates the enantioselective step.

1.2.1 Allylic Alcohols

The field of allylic alcohol substitution has traditionally been dominated by Lewis acid and transition metal catalysis.[38–41] Over the years, this synthetic strategy has been shown to provide one of the most powerful and efficient methods for the formation of carbon–carbon and carbon–heteroatom bonds. Limited attention, however, has been

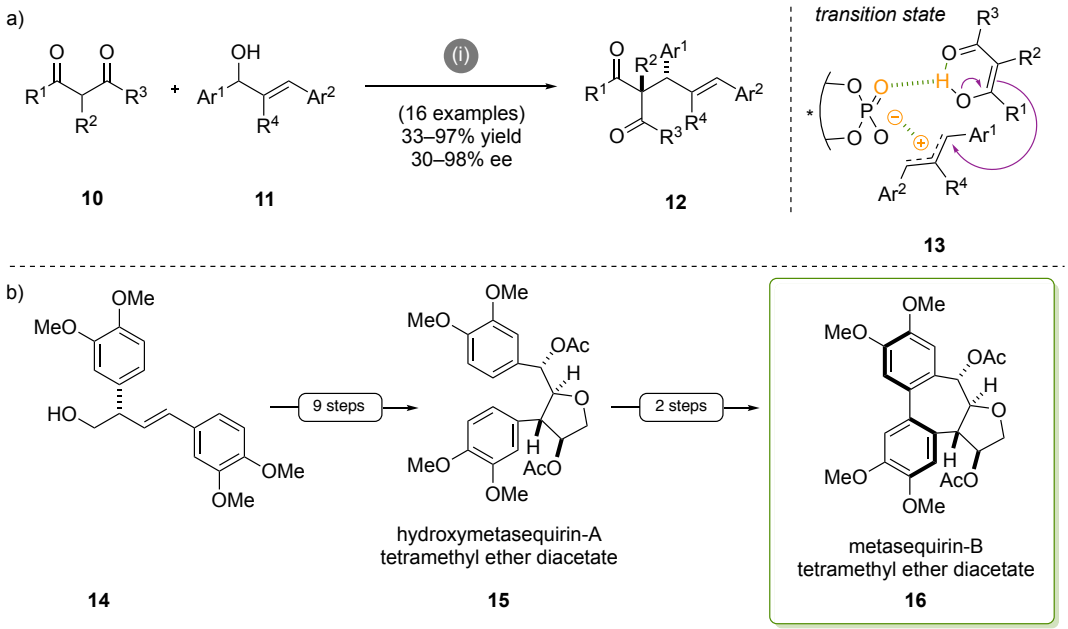
paid to Brønsted acid-mediated reactions of the compound class as a result of the hydroxyl moiety often being viewed as a poor leaving group.

One of the first asymmetric allylic substitution reactions mediated by a chiral phosphoric acid was reported by Rueping *et al.* (Scheme 1.3).[42] In the presence of **BA34** (5–10 mol%), a variety of *o*–allylic alcohol–substituted phenols **7** were shown to efficiently cyclise to the corresponding 2*H*–chromenes **8** in 61–95% yield and with 84–96% ee. The reaction mechanism was postulated to involve initial protonation of the substrate that resulted in its dehydration. Nucleophilic attack of the phenolic oxygen onto the allylic cation in this intimate ion–pair species was then surmised to provide the enantioenriched 2*H*-chromene **8**. This proposed mechanism was further supported by control experiments that showed the products obtained from enantioenriched starting materials to relinquish all stereochemical information when exposed to an achiral Brønsted acid catalyst. The formation of transition state **9**, comprised of the carbocationic species and the phosphoramidate anion along with the phenolic O–H hydrogen bonding with the catalyst, was subsequently proposed.



Scheme 1.3: Asymmetric Brønsted acid–mediated contact ion pair allylic substitution of *o*–allylic alcohol–substituted phenols **7** to 2*H*–chromenes **8**. i) **BA34** (5-10 mol%), toluene, –78 °C.

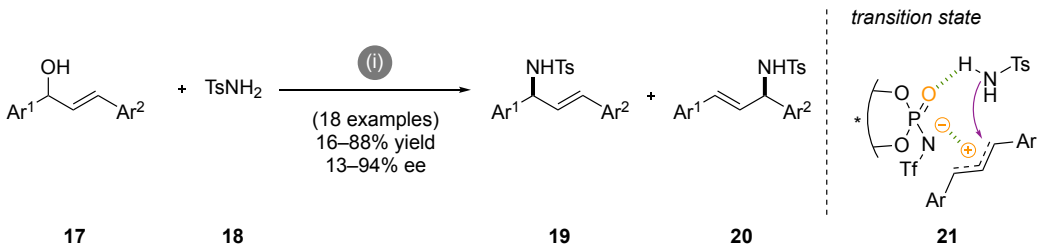
Following this study, the Gong group reported the allylation of 1,3–dicarbonyl compounds **10** by allylic alcohols **11** (Scheme 1.4a).[43] The corresponding substitution products **12** were furnished *via* the bifunctional–activation–type transition state **13** in 33–97% yield and with 30–98% ee. This method was applied to the total synthesis of



Scheme 1.4: (a) Asymmetric Brønsted acid–mediated allylic alkylation of alcohol **11** with 1,3–dicarbonyl **10** to dicarbonyls **12**. i) **BA24** (10 mol%), DCE, –20 °C, 36 h. (b) Application of the former protocol to the metasequirins **15** and **16**. Ar = 3,4–$(OMe)_2C_6H_5$.

two members of the metasequirin family (Scheme 1.4b). The first, hydroxymetasequirin A tetramethyl ether diacetate **15**, was accessible in 9 steps from the alkene **14**, a further two steps were shown to complete the synthesis of metasequirin B tetramethyl ether diacetate **16** in 10% yield over 11 steps.

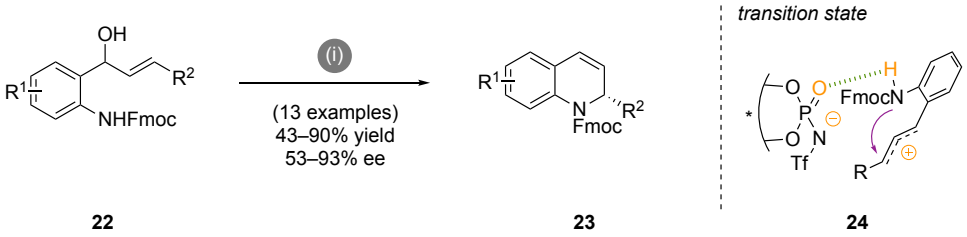
Concurrently, Du *et al*. showed that the enantioselective chiral phosphoric acid–mediated allylic amination of allylic alcohols **17** could be achieved with $TsNH_2$ to afford the allylic amines **19** and **20** (Scheme 1.5).[44] In this study, the Brønsted acid



Scheme 1.5: Asymmetric Brønsted acid–mediated intermolecular allylic amination of alcohol **17** with sulphonamide **18** to allylic amines **19** and **20**. i) **BA11** (10 mol%), $CHCl_3$, –60 °C, 10 h.

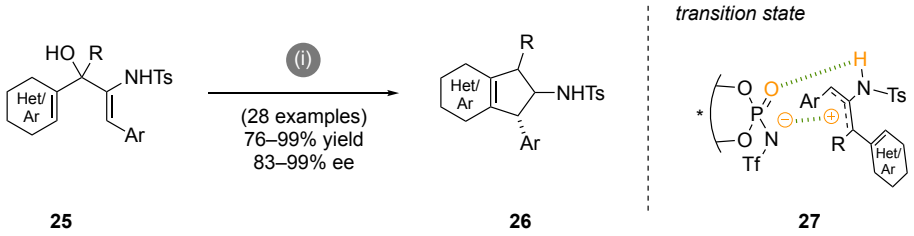
BA11 was found to form the optimum ion pair species with the carbocationic intermediate for efficient enantio–induction in the proposed transition state **21**. This furnished the allylic amines **19** and **20** in 16–88% yield with ee values of 13–94%. The regioselectivity of this transformation was found to be highly influenced by the electronic nature of aryl substituents present on the allylic alcohol **17**.

Building on this work, Xie and Zhou reported the synthesis of the 1,2–dihydroquinolines **23** that relied on the chiral Brønsted acid-mediated allylic amination of allylic alcohols **22** (Scheme 1.6).[45] In the presence of chiral *N*–phosphoramide **BA34**, this enantioselective method provided the 2*H*–quinolines in 43–90% yield and with 53–93% ee *via* the purported carbocation–catalyst ion pair transition state **24**.



Scheme 1.6: Asymmetric Brønsted acid–mediated intramolecular allylic amination of alcohol **21** to 2*H*–quinolines **22**. i) **BA34** (10 mol%), DCM/PhH (1:1), –20 °C, $MgSO_4$ (72 mg/0.1 mmol), 3–5 days.

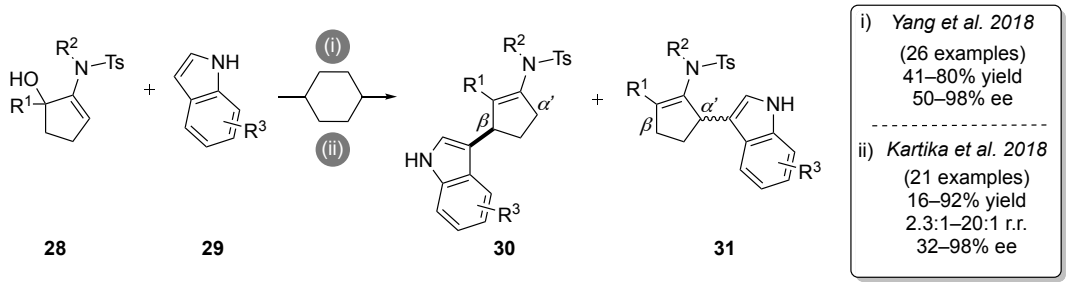
At about the same time, Chan and co–workers described the chiral Brønsted acid-mediated enantioselective dehydrative Nazarov–type electrocyclisation of *β*–amino-2-en-1-ols **25** (Scheme 1.7).[46] With (*S*)–**BA21** as the catalyst, this enantioselective method provided a facile synthetic route to 1*H*–indenes and 4*H*–cyclopenta[*b*]thiophenes in 76–99% yield and with ee values of 83–99%. Both experimental and computational studies supported the hypothesis that a contact ion pair species, in conjunction with H–bonding, to be operative in the proposed dual–activation transition state **27**. As a consequence, the transfer of stereochemical



Scheme 1.7: Asymmetric Brønsted acid–mediated Nazarov–type electrocyclization of allylic alcohol **25** to indene **26**. i) (*S*)–**BA21** (5 mol%), 4 Å MS, toluene, 0.05 M, at RT for 0.5 h, or at –60 °C for 36 h.

information from the catalyst to the substrate was thought to occur simultaneously with the 4π–electrocyclization.

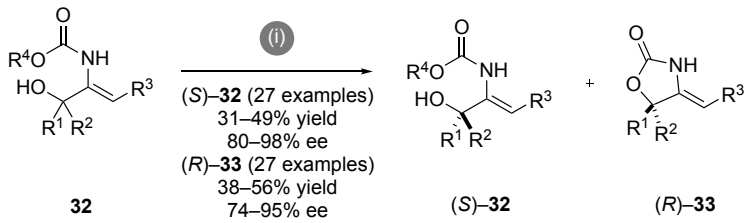
In the same year, the groups of Yang and Kartika independently reported the enantioselective Brønsted acid–mediated synthesis of β–indolyl cyclopentenamides **30** (Scheme 1.8).[47,48] Yang *et al.* reported the SPINOL–derived phosphoric acid catalyst **BA40** to provide the optimum combination of selectivity and reactivity for the asymmetric addition of indoles **29** to α–hydroxylcyclopentenamides **28**. These reaction conditions provided the β–addition adducts **30** in 41–80% yield and with 50–98% ee after separation of the α'–addition by–product **31**. Kartika and co–workers found the optimum conditions to involve the BINOL–derived CPA catalyst **BA6**.



Scheme 1.8: Enantioselective Brønsted acid–mediated synthesis of β–indolyl cyclopentenamides **28** independently with indoles **29** reported by both Yang *et al.* and Kartika *et al.* Yang's optimised conditions, i) **BA40** (10 mol%), **29** (1.5 eq.), toluene, 45 °C, 12 h. Kartika's optimised conditions, ii) **BA6** (10 mol%), 28 (1.0 eq.), DCE, 4 Å MS, –5 °C to –10 °C, 48 to 65 h.

These conditions furnished a mixture of both β– and α'–addition products **30** and **31** in 16–92% combined yield and with regioisomeric ratios (rr) of 2.3:1–20:1 along with ee values of **30** of 32–98%.

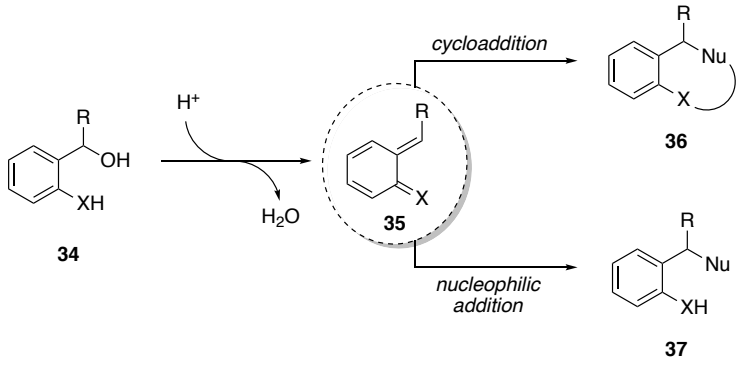
More recently, Yang and co–workers reported the Brønsted acid–mediated kinetic resolution of tertiary–substituted allylic alcohols **32** (Scheme 1.9).[49] This protocol was found to provide access to enantioenriched 1,2–amino alcohols (*S*)–**32** and the transesterification products (*R*)–**33**. In this study, the optimum reaction conditions for the kinetic resolution was achieved with **BA26** as the catalyst, which provided the two enantioenriched compounds in 31–56% yield and with 74–98% ee.



Scheme 1.9: Brønsted acid–mediated kinetic resolution of tertiary–substituted allylic alcohols 32. i) BA26 (10 mol%), PhCl, 5 Å MS, 0 °C to 25 °C, 48 to 65 h.

1.2.2 Benzylic Alcohols

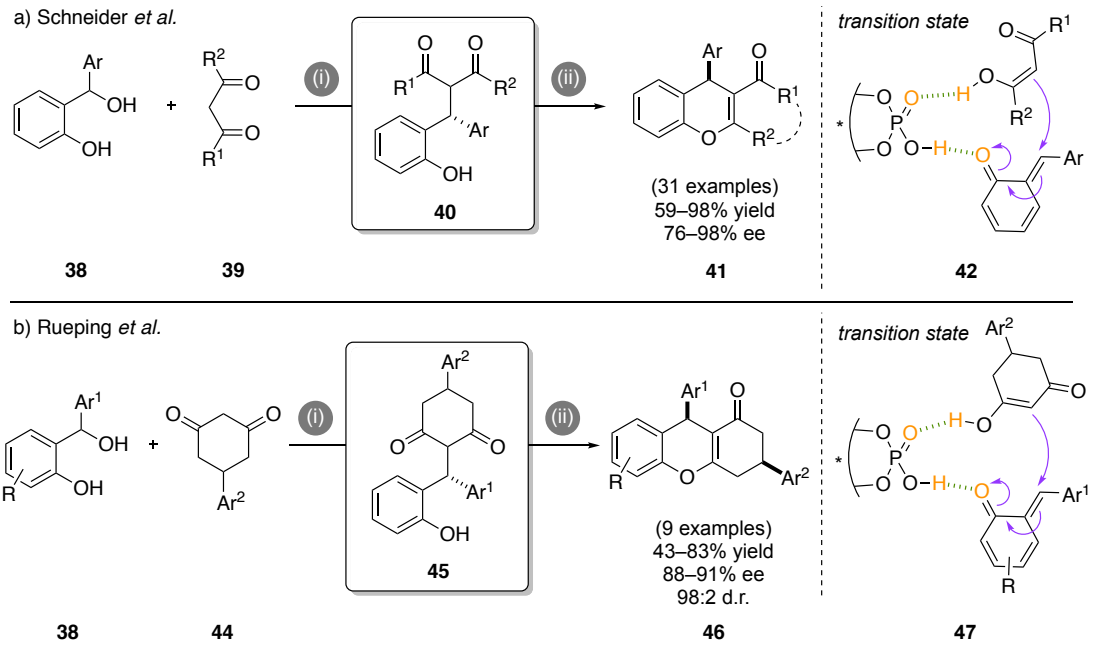
Within the field of chiral Brønsted acid catalysis, reactions that make use of *o*–hydroxybenzyl alcohols **34** have gained an increasing amount of attention over recent years. The driver of this chemistry has been the ease in which the substrates can be converted to the highly reactive *o*–quinone methide (*o*–QM) resonance structure **35** as a result of dehydration in the presence of a chiral phosphoric acid catalyst (Scheme 1.10). The shepherding of this postulated reactive species in functional group transformations such as nucleophilic addition and [$n + m$] cycloaddition involving the conjugate base of the chiral catalyst provides an array of enantioenriched synthetic targets.[50,51]



Scheme 1.10: Generation and utilisation of *o*–QM mediated by Brønsted acid catalysis. (X = O,N)

1.2.2.1 Nucleophilic Additions

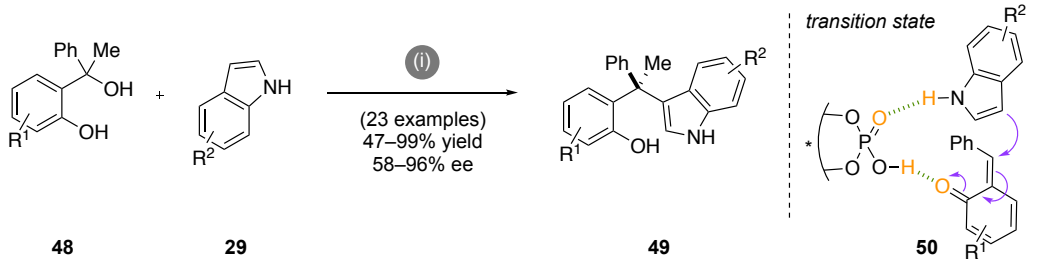
In 2014, the groups of Schneider and Rueping concurrently reported the enantioselective addition of 1,3–dicarbonyl compounds **39** and **44** to *o*–QM **38** mediated by a chiral Brønsted acid catalyst (Scheme 1.11).[52,53] These transformations afforded the 4*H*-chromene derivatives **41** and **46** in yields and ee values of up to 98%. In the case of the tricyclic adducts, dr values of up to 98:2 were also obtained. In both



Scheme 1.11: Asymmetric addition of 1,3–dicarbonyl compounds **39** or **44** to *o*–hydroxybenzyl alcohols **38** to *O*–heterocycles **41** and **46**. a) (i) **BA25** (5 mol%), $CHCl_3$. (ii) *p*–TsOH, 40 °C, $CHCl_3$. b) (i) **BA24** (5 mol%), $MgSO_4$, PhMe, –20 °C. (ii) $FeCl_3$ (10 mol%), RT, 4 Å MS.

works, the mechanism for the transformations were reasoned to begin with the protonation of the *o*-hydroxybenzyl alcohol **38** by the Brønsted acid catalyst. The reactive *in situ* generated *o*–QM species was proposed to undergo nucleophilic attack by the respective 1,3–dicarbonyl compounds **39** and **41** to afford the addition products **40** and **45**. The *p*–TsOH and $FeCl_3$ co–catalysts employed in these works was proposed to promote cycloaddition of these respective adducts to provide the corresponding 4–aryl–4*H*–chromin and tricyclic tetrahydroxanthene products. For the 4–aryl–4*H*–chromin adduct, the proposed involvement of the intermediate **40** was supported by its isolation. The preservation of the enantiomeric excess value of this intermediate to the product also implied the enantio–determining step to be the initial nucleophilic attack by the 1,3–dicarbonyl compound onto the *o*–QM species.

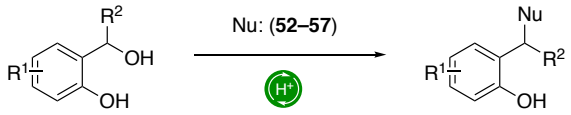
Following this study, the Sun group described an expedient method for the construction of indoles containing an all–carbon quaternary stereocentre from tertiary *o*–hydroxybenzyl alcohols **48** and indoles **29** mediated by chiral Brønsted acid catalysis (Scheme 1.12).[54] The reaction mechanism was proposed to proceed *via* the transition state **50** in which the chiral Brønsted acid catalyst interacts simultaneously with the *in situ* generated *o*–QM species and H–bonding interactions with the indole derivative. Achieving product yields up to 99% and ee values of up to 96%, control



Scheme 1.12: Brønsted acid–mediated enantioselective addition of indoles **29** with *o*–hydroxybenzyl alcohols **48** indole **49**. (i) **BA38** (10 mol%), DCE, 0 °C, 48 h.

experiments showed that the presence of the phenolic hydroxy group and an electron–donating group *para* to the benzylic alcohol were crucial for both reactivity and selectivity. Removal of the electron–donating group or protection of the phenolic alcohol led to a significant decrease in both product yield and ee value. Furthermore, protection of the indole **29** as the *N*–methyl derivative was reported to lead to isolation of only the E1 reaction product. This supported the hypothesis of the involvement of the H–bonded transition state **50** directing the enantioselective nucleophilic attack onto the *o*–QM species. On the basis of this concept, a number of research groups have extensively explored the reaction chemistry of *o*–QM intermediates with other Brønsted acid–compatible nucleophiles that are able to partake in H–bonding (Table 1.1).

Table 1.1: Brønsted acid–mediated enantioselective substitutions of *o*–hydroxybenzyl alcohols **52**.



38 **51**

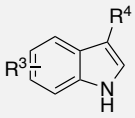
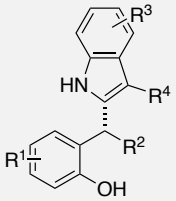
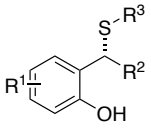
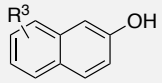
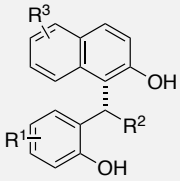
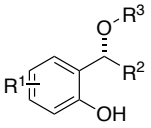
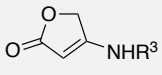
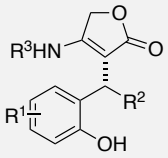
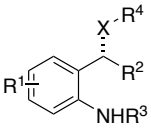
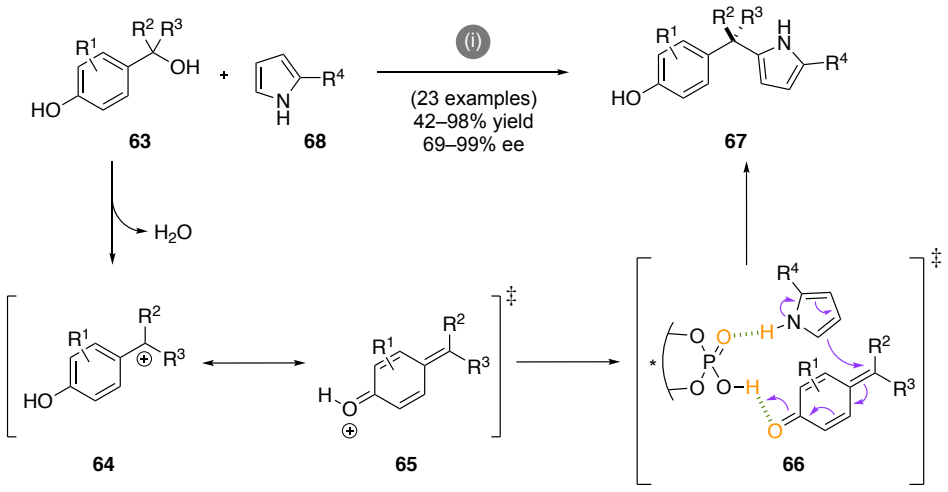
entry	nucleophile	catalyst	product	details	reference
1	 R ≠ H **52**	**BA32**	 **57**	49 examples 45–99% yield 80–98% ee	55
2	R3-SH **53**	**BA36**	 **58**	11 examples 67–83% yield 4–84% ee	56

Table 1.1 continued

entry	nucleophile	catalyst	product	details	reference
3	 **54**	**BA25**	 **59**	13 examples 90–95% yield 74–98% ee	57
4	R^3-OH **55**	**BA36**	 **60**	24 examples 65–95% yield 70–92% ee	58
5	 **56**	**BA24**	 **61**	19 examples 52–89% yield 74–90% ee	59
6	R^4-XH X = O, S **55** / **53**	**BA29**	 **62**	36 examples 30–98% yield 72–98% ee	60

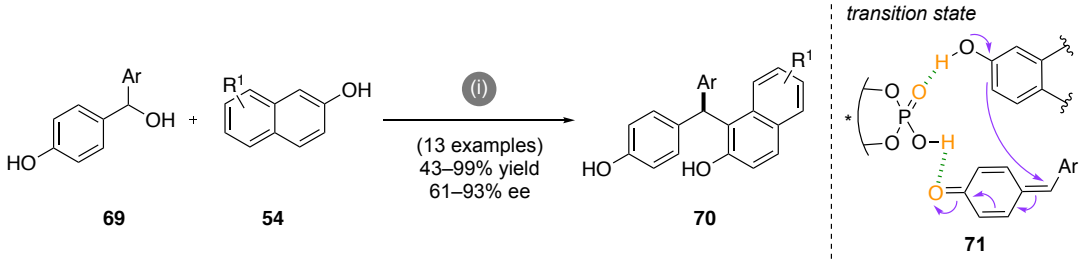
Akin to the *o*–hydroxybenzyl alcohols **38**, the *p*–hydroxybenzyl alcohols **63** have also been reported to form the corresponding *p*–quinone methides (*p*–QM) species **64** *via* a dehydrative isomerisation process under acidic conditions. In an initial study by Sun and co–workers, the enantioselective reaction of pyrroles **68** with *p*–hydroxybenzyl alcohols **63** was found to provide a range of 1,6–conjugate addition products **67** in 42–98% yield with ee values of 69–99% (Scheme 1.13).[61] The transformation was proposed to proceed *via* a mode of activation in which both the *p*–QM species and the pyrrole compound simultaneously coordinated to the chiral Brønsted acid catalyst to form the transition state **66**. This was the active species that was thought to be



Scheme 1.13: Brønsted acid–mediated asymmetric addition of pyrroles **68** with *p*–hydroxybenzyl alcohols **63** to **67**. (i) **BA38** (5 mol%), $CHCl_3$, 3 Å MS, 0 °C, 48 h.

responsible for the stereoselective addition of the pyrrole to the *p*–QM adduct to deliver the enantioenriched product.

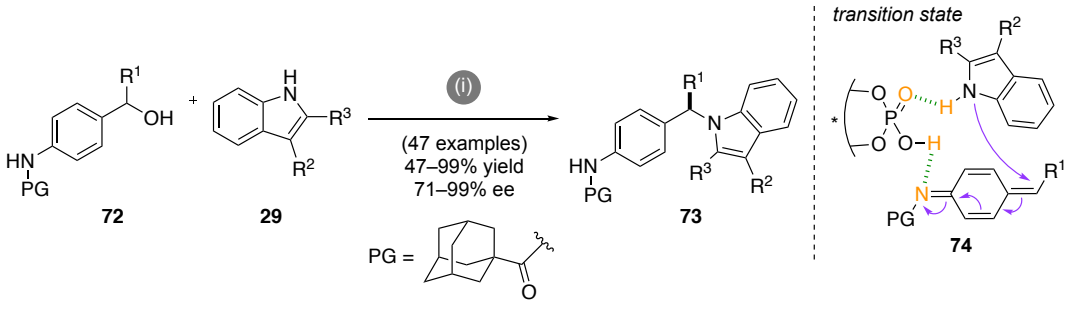
Sun *et al.* extended the synthetic approach to include the chiral Brønsted acid–mediated additions of naphthols **54** to *p*–hydroxybenzyl alcohols **69** (Scheme 1.14).[62] In the presence of the SPINOL–derived Brønsted acid (*S*)–**BA38**, the 1,6–conjugate addition of the naphthol to the *in situ* generated *p*–QM species furnished the triarylmethane product **70** in 43–99% yield and with 61–93% ee. In line with their previous reports, the transfer of stereochemical information was thought to derive from the formation of the bifunctional–activated transition state **71** in which both the *p*–QM species and the naphthol were H–bonded to the chiral Brønsted acid catalyst. This



Scheme 1.14: Brønsted acid–mediated asymmetric addition of naphthols **54** with *p*–hydroxybenzyl alcohols **69** to **70**. i) (*S*)–**BA38** (10 mol%), CPME, 4 Å MS, RT, 72 h.

methodology was found to be limited to 2–naphthols as reactions with 1–naphthols were shown to give good to excellent product yields but with moderate ee values.

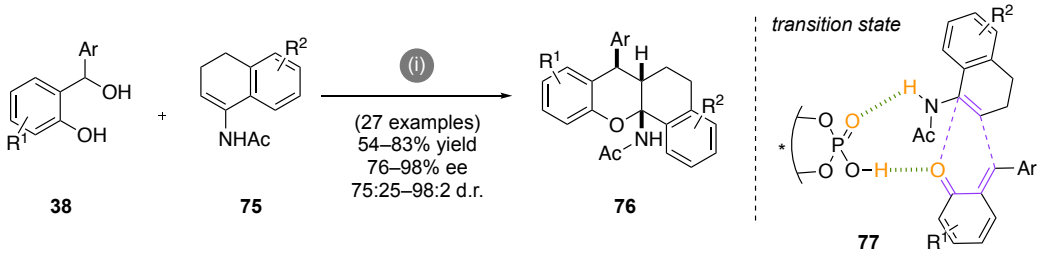
Building on this study, the asymmetric 1,6–conjugate addition to an *aza–p*–QM species, generated *in situ* from the corresponding *p*-aminobenzyl alcohols **72**, by substituted indoles **29** was reported by the Sun group.[63] Employing the pyrenyl–substituted chiral Brønsted acid (*S*)–**BA39** as the catalyst, the method was shown to afford the *N*–alkylation product **73** in 47–99% yield with ee values of 71–99% (Scheme 1.15). It was found that the selection of the *N*–protecting group in **72** was essential for the selectivity at the new C–N bond. Added to this, the involvement of the reputed *aza–p*–QM intermediate was supported in a control experiment demonstrating that a *N,N*–disubstituted *aza–p*–QM species led to no reaction under the standard reaction conditions. The observed ee values obtained in this study were also proposed to be due to the transition state **74** in which the chiral Brønsted acid catalyst performs a bifunctional role, simultaneously activating the *aza–p*–QM species and the indole.



Scheme 1.15: Brønsted acid–mediated asymmetric *N*–alkylation of indoles **29** through 1,6–conjugate addition with *p*–aminobenzyl alcohols **72** to **73**. i) (*S*)–**BA39** (10 mol%), PhMe, 5 Å MS, RT, 36 h.

1.2.2.2 Cycloadditions

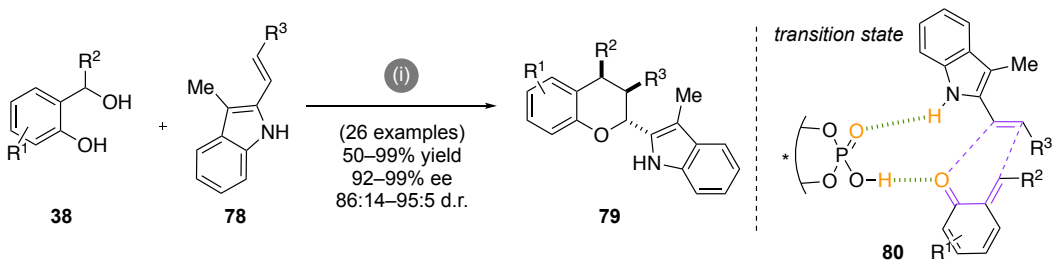
Schneider and Saha documented one of the first examples of *o*–QM intermediates in works examining the chiral Brønsted acid–catalysed formal [4 + 2] cycloaddition of



Scheme 1.16: Brønsted acid–mediated asymmetric addition of enamides **75** with *o*–hydroxybenzyl alcohols **38** to *o*–heterocycles **76**. i) **BA7** (5 mol%), DCM, 4 Å MS, RT.

o–hydroxybenzyl alcohols **38** with enamides **75** (Scheme 1.16).[64] A broad range of acetamidotetrahydroxanthenes **76** were furnished in 54–83% yield and with 76–98% ee and diastereomeric ratios of up to 98:2. The mechanism was thought toinvolve Brønsted acid–catalysed dehydration of the *o*–hydroxybenzyl alcohol **38** to give the *o*–QM species. Its involvement with the enamide and catalyst in the bifunctional transition state **77** was reported to be crucial in the enantioselective cycloaddition step. The versatility of the synthetic method was demonstrated by the conversion of a number of the *o*–heterocyclic products to the corresponding chromene derivatives through Brønsted acid–catalysed elimination of the acetamide with retention of optical purity.

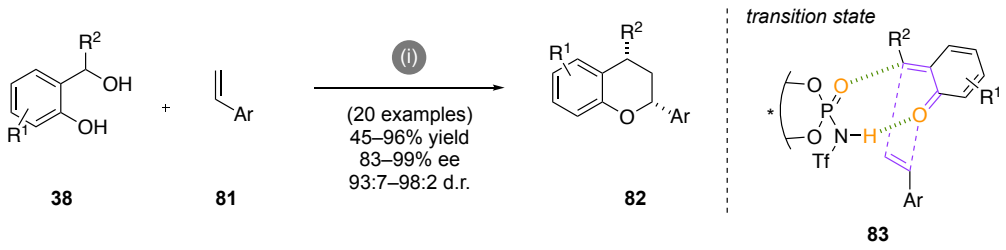
At about the same time, the asymmetric inverse–electron–demand *oxa*–Diels–Alder reaction of 3–methyl–2–vinylindoles **78** and *o*–QM species generated *in situ* from *o*–hydroxybenzyl alcohols **38**, was reported by the Shi group (Scheme 1.17).[65] This



Scheme 1.17: Brønsted acid–mediated asymmetric *oxa*–Diels–Alder of *o*–hydroxybenzyl alcohols **38** with 3-methyl–2–vinylindoles **78** to indole–substituted chromanes **79**. i) **BA4** (10 mol%), DCE, 25 °C, 12 h.

synthetic method furnished a range of enantioenriched chromans **79** featuring three neighbouring stereogenic centres in 50–99% yield and with ee values of 92–99% and good dr values of up to 95:5. Control experiments also confirmed the necessity to use C3–substituted indoles so as to prevent addition of the nucleophile at this position. The proposed reaction mechanism was thought to involve the chiral Brønsted acid catalyst **BA4** playing a bifunctional role in the transition state **80** by H–bonding to both the *o*–QM species and the dienophile during the enantio–determining step. In addition, (*Z*)–vinylindoles were shown to isomerise to the (*E*)–alkene under the reaction conditions with no loss in stereoselectivity, albeit with a decrease in reactivity.

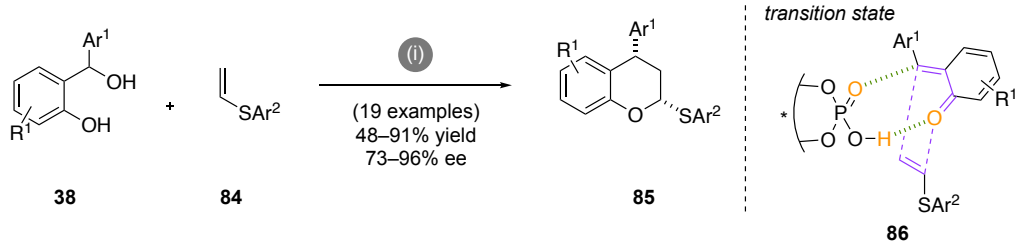
In the same year, Rueping and co–workers detailed the chiral Brønsted acid–mediated cycloaddition of *o*–hydroxybenzyl alcohols **38** with unactivated alkenes **81** (Scheme 1.18).[66] The phosphoramide–based acid catalysts were found to be more suitable than their phosphoric acid counterparts for this transformation. In the presence of the catalyst **BA30**, the reaction furnished a range of chromanes **82** in 45–96% yield and with 83–99% ee and up to 98:2 dr. The hypothesised reaction mechanism was surmised to proceed with the chiral Brønsted acid catalyst acting as a dual–activator in the transition state **83** that interacted with the substrates through H–bonding and ion pairing. As a consequence, this allowed the aryl alkene to initiate cycloaddition by



Scheme 1.18: Brønsted acid–mediated asymmetric cycloaddition of *o*–hydroxybenzyl alcohols **38** with unactivated alkenes **81** to chromanes **82**. i) **BA43** (5 mol%), PhMe, 4 Å MS, –60 °C.

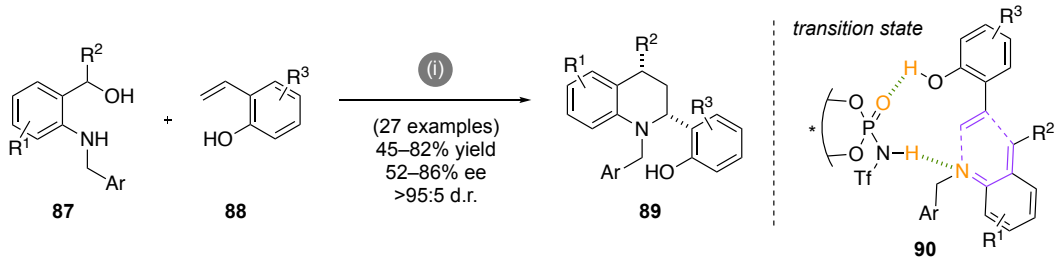
approaching the complex in an *endo* fashion to afford the corresponding *o*–heterocycle **82**.

The Sun group reported the analogous chiral Brønsted acid–mediated [4 + 2] cycloaddition of *o*–hydroxybenzyl alcohols **38** and vinyl sulphides **84** (Scheme 1.19).[67] The asymmetric transformation was shown to proceed to afford a range of enantioenriched chromanes **85** in 48–91% yield with ee values of 73–96%. In a similar manner to the study by the Rueping group, the postulated mechanistic pathway was reasoned to involve both H–bonding and ion–pair interactions of the substrates with the chiral Brønsted acid catalyst. The utility of the newly installed sulphenyl group in the product was also demonstrated by its ease of removal to provide access to a range of substituted chromanes.



Scheme 1.19: Brønsted acid–mediated asymmetric cycloaddition of *o*–hydroxybenzyl alcohol **38** and vinyl sulphide **84** to chromanes **85**. i) **BA28** (10 mol%), DCM (0.05 M), 4 Å MS, –20 °C, 96 h.

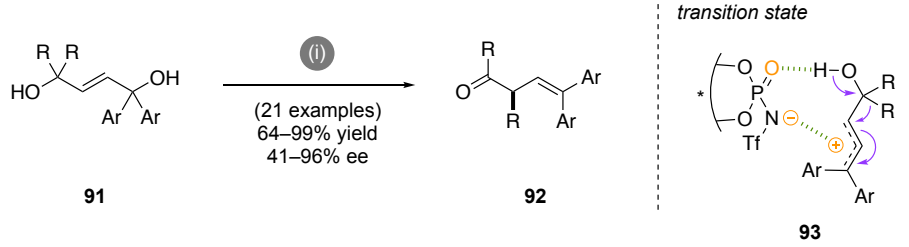
In a subsequent study by Shi *et al.*, it was demonstrated that the chiral Brønsted acid catalytic [4 + 2] cycloaddition of *in situ* generated *o*–QM species, formed *in situ* from *o*–aminobenzyl alcohol **87**, and *o*–hydroxystyrenes **88** (Scheme 1.20).[68] In the presence of the phosphoramide catalyst **BA27**, the corresponding enantioenriched tetrahydroquinolines **89** possessing two chiral centres were furnished in 45–82% yield and with 52–86% ee and with dr values of ≥95:5. A limitation of the synthetic method, however, was. the need for the presence of the *o*–hydroxy group as no reaction was



Scheme 1.20: Brønsted acid–mediated asymmetric cycloaddition of *o*–aminobenzyl alcohol **87** and *o*–hydroxystyrenes **88** to quinolines **89**. i) **BA27** (10 mol%), $CHCl_3$, 5 Å MS, 25 °C, 48 h.

found in a control experiment using a methyl–protected *o*–hydroxystyrene under the standard reaction conditions. Added to this, no reaction was reported for styrene substrates possessing either a hydroxyl or *p*–substituted motif while those without the functional group gave product yields of 40–43% and with 44–58% ee and dr values of ≥95:5. On the basis of these findings, it was suggested that whilst the *o*–hydroxy group did not influence reactivity, it played a pivotal role in the transition state **90**. Tentatively, this could be due to H–bonding interactions between the substrate and the CPA so as to provide efficient transfer of stereochemical information.

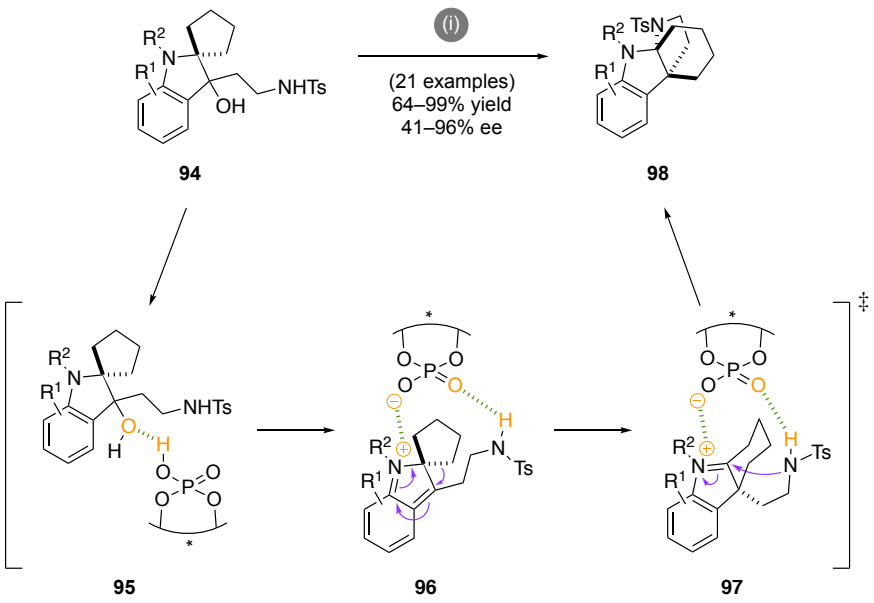
Zhu and co–workers developed a chiral Brønsted acid–mediated asymmetric Pinacol rearrangement of vinyl diols **91** as an efficient approach to *β,γ*–unsaturated ketones **92** (Scheme 1.21).[69] In this work, the transformation of 21 examples catalysed by the BINOL–derived *N*–triflyl phosphoramide **BA27**, was shown to deliver the ketone product in yields of 64–99% and with 41–96% ee. The reaction mechanism put



Scheme 1.21: Brønsted acid–mediated asymmetric Pinacol rearrangement of vinyl alcohol **91** to ketones **92**. i) **BA27** (10 mol%), MTBE, 4 Å MS, –20 °C, 12 h.

forward involved initial Brønsted acid–catalysed dehydration to provide the transition state **93**. The hypothesised H–bonding and ion–pair interactions between the catalyst anion and the remaining hydroxyl group and allylic carbocationic motif of the substrate was proposed to form an intimate chiral environment for the enantioselective 1,2–shift to occur.

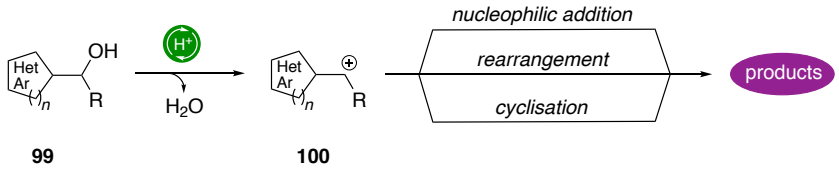
In a recent study, Zu and co–workers described the first chiral Brønsted acid–mediated enantioselective *aza*–Pinacol rearrangement (Scheme 1.22).[70] The SPINOL–derived **BA42**–catalysed protocol was found to be an efficient approach to the indoline structure **98**, affording yields of 64–99% and with ee values of 41–96%. Mechanistically, it was proposed that on the formation of the H–bonded species **95**, Brønsted acid–assisted dehydration of the tertiary alcohol led to cationic dual–activated species **96**. An enantioselective 1,2–shift was proposed to produce the *aza*–Pinacol rearrangement intermediate **97**, which underwent cyclisation to furnish the fused indoline product **98**.



Scheme 1.22: Brønsted acid–mediated asymmetric *aza*–Pinacol rearrangement of alcohol **94** to indolines **98**. i) **BA45** (20 mol%), DCE, 4 Å MS, 0 °C, 12 h.

1.2.3 Heteroaryl Alcohols

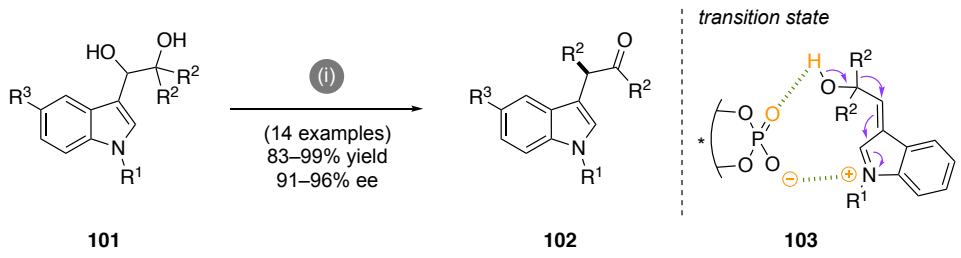
Heteroaryl–substituted carbinols **99** have been shown in a number of studies to serve as electrophiles due to their ability to be readily activated by a chiral Brønsted acid (Scheme 1.23). This is thought to be a result of stabilisation of the positive charge by the heteroaryl motif through resonance in the ensuing carbocationic intermediate



Scheme 1.23: General Brønsted acid–mediated reactivities of heteroaryl alcohols 99.

100.[71] As a consequence, this stability enables an extended interaction between the cationic intermediate and the counteranion and, thus, the potential of enhancing enantioinduction in its following transformations.

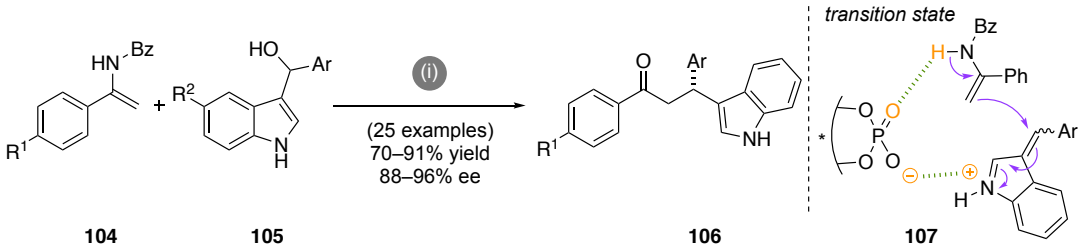
One of the seminal works exploiting this mode of reactivity was described by Antilla *et al.* in a study reporting the asymmetric Pinacol rearrangement of indolyl diols **101** mediated by a chiral phosphoric acid (Scheme 1.24).[72] The protocol was found to provide an expedient approach to a wide variety of α–indolyl ketones **102** in 83–99% yield and with 91–96% ee. A plausible reaction mechanism was described to initially involve Brønsted acid–mediated dehydration to provide the dual–activation–type



Scheme 1.24: Brønsted acid–mediated Pinacol rearrangement of indolyl diols 101 to α–indolyl ketones 102. (i) BA30 (2.5 mol%), 4 Å MS, PhH, RT, 6 h.

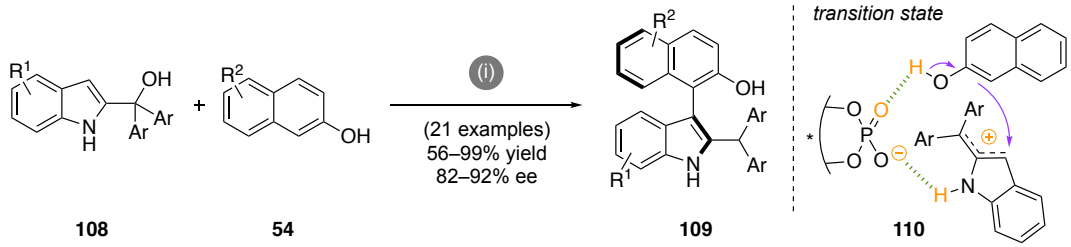
transition state **103**. A subsequent [1,2]–aryl shift was then reasoned to complete the Pinacol rearrangement to furnish the enantioenriched ketone product.

At about the same time, the Gong group delineated the enantioselective alkylation of enamides **104** by indolyl alcohols **105** (Scheme 1.25).[73] The asymmetric reaction was reported to afford a broad range of enantioenriched *β*–aryl–3–(3–indolyl)propanones **106** in yields and with ee values of 70–91 and 88–96%. Mechanistically, it was proposed that an initial Brønsted acid–mediated dehydration of indole **105** and its subsequent interaction with enamide **104** generated the transition state **107**. This was thought to involve H–bonding and ion–pair interactions of the cationic indolyl species with the conjugate base of the catalyst. As a result, it was proposed that this provided the chiral environment for the alkylation or conjugate addition to occur, which, on hydrolysis, furnished the desired enantioenriched *β*–indolyl ketone product.



Scheme 1.25: Brønsted acid–mediated alkylation reaction of enamides **104** by indolyl alcohols **105** to *β*–aryl–3–(3–indolyl)propanones **106**. (i) **BA31** (10 mol%), DCM, –30 °C.

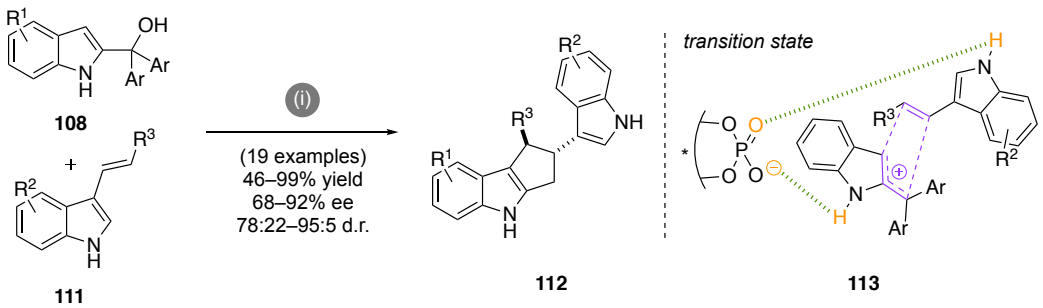
In recent work by Shi and co–workers, the enantioselective synthesis of axially chiral naphthyl–indoles **109** from CPA–mediated addition of naphthols **54** with indolyl methanols **108** was described (Scheme 1.26).[74] Achieving product yields and ee values of 56–99 and 82–92%, respectively, the reaction mechanism was postulated to be initiated by Brønsted acid–catalysed dehydration of 2–indolylmethanol **108**. Its



Scheme 1.26: Brønsted acid–mediated enantioselective synthesis of axially chiral naphthyl–indoles **109** from indolyl methanols **108** and 2–naphthols **54**. (i) (*S*)–**BA29** (10 mol%), 3 Å MS, toluene, 0 °C.

subsequent interaction with the naphthol **54** and catalyst was thought to give the dual–activation–type transition state **110**. Nucleophilic addition of the naphthol, followed by rearomatisation was proposed to afford the biaryl–product. The absence of reaction and the formation of the product in low yield and ee for the respective control experiments with methyl–protected 2–naphthol and *N*–methyl–1*H*–indole was put forward as support for the involvement of dual activation in the transition state.

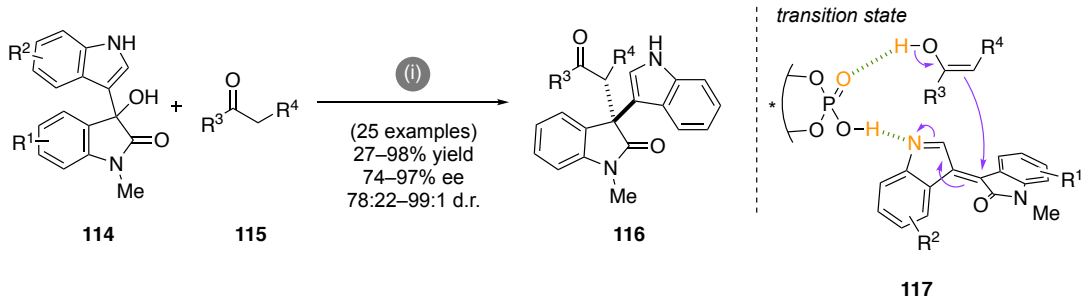
In 2016, the chiral Brønsted acid–mediated asymmetric [3 + 2] cycloaddition of C3–unsubstituted 2–indolylmethanols **108** with 3–vinylindoles **111** was realised by the Shi group (Scheme 1.27).[75] The synthetic method was shown to efficiently construct a variety of cyclopenta[*b*]indoles **112** in 46–99% yield and with 68–92% ee and dr of up to 95:5. In this work, protection of indole nitrogen in **108** or **111** was reported to either significantly reduce the enantioselective outcome of the transformation or led to no



Scheme 1.27: Brønsted acid–mediated asymmetric [3 + 2] cycloaddition of 2–indolylmethanols **108** with vinyl indoles **111** to cyclopenta[*b*]indoles **112**. (i) **BA41** (5 mol%), toluene, 90 °C.

reaction. It was found that only tertiary 2–indolylmethanols would react under the standard conditions, which was reasoned to be due to stabilisation of the reputed carbocationic intermediate being insufficient with secondary alcohol substrates. Added to this, the reaction mechanism put forward was proposed to involve the chiral phosphoric acid catalyst playing a bifunctional role by H–bonding to the N–H groupof both substrates. This provided the requisite chiral environment for regio– and enantioselective cycloaddition to occur to afford the cyclopenta[*b*]indole product.

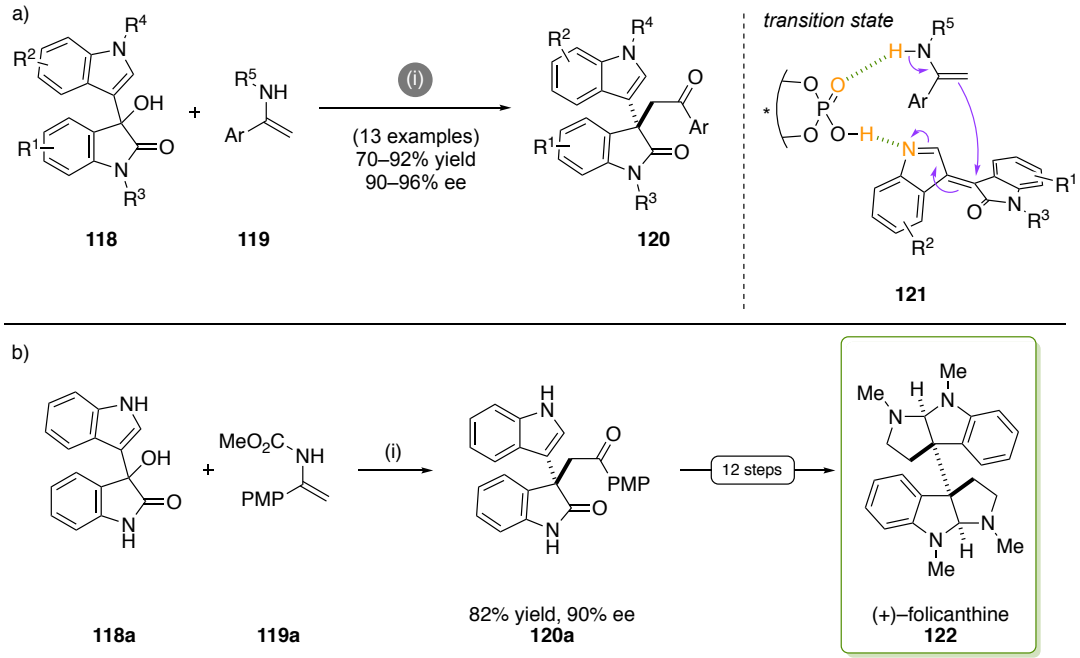
The Peng group reported the chiral Brønsted acid–mediated direct alkylation of ketones **115** with 3–hydroxy–2–oxindoles **114** to furnish the α–alkylation products **116** in 27–98% yield and with 74–97% ee and up to 99:1 dr (Scheme 1.28).[76] With initial attempts to employ 3–indolylmethanols shown to be unsuccessful, it was reasoned that the more electrophilic alcohol analogue would be a better alkylating reagent. In a control experiment, the analogous reaction of a Bn–protected indole showing the delivery of the corresponding product in a lower yield and ee value was put forward as support for the involvement of the transition state **117**. It was proposed that the Brønsted acid catalyst might preferentially engage in H–bonding interactions with the vinylogous indolyl species and the enol isomer of the ketone that results in the latter adding to the *re* face of the former to afford the alkylated (*R*)–adduct **116**.



114 **115** **116** **117**

Scheme 1.28: Brønsted acid–mediated asymmetric direct α–alkylation of 3–hydroxy–2–oxindole **114** with ketones **115** to α–alkylation products **116**. (i) **BA19** (10 mol%), toluene, –15 to 0 °C, 48 h.

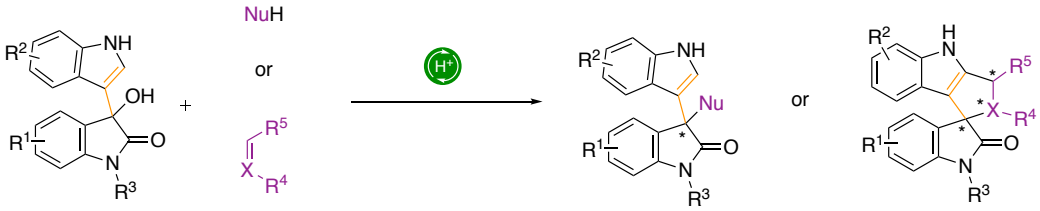
In the same year, Gong and co–workers described the chiral phosphoric acid–mediated enantioselective nucleophilic substitution reaction of 3–hydroxyoxindoles **118** with enecarbamates **119** (Scheme 1.29).[77] This method provided an expedient synthetic route to 3,3'–disubstituted oxindoles **120** with a range of substitution patterns in 70–92% yield and with ee values of 90–96% ee. As part of this study, density functional theory calculations revealed that the reaction was likely to proceed *via* a sequential dehydration–Michael addition pathway. The chiral Brønsted acid was proposed to initiate the dehydration and H–bond to the resulting iminium species along with the enamine to form the transition state **121**. Subsequent addition to the activated enecarbamate to the *si* face of the *N*–heterocycle followed by hydrolysis was described to furnish the alkylated (*S*)–adduct **120**. The utility of this protocol was also demonstrated by conversion of one example to the natural product (+)–folicanthine **122** in 12 steps with an overall yield of 3.7%.



Scheme 1.29: a) Brønsted acid–mediated substitution of 3–hydroxyoxindoles **118** with enamines **119** to alkylated adducts **120**. (i) **BA8** (10 mol%), Na_2SO_4, DCM. b) Application of the present protocol to the total synthesis of (+)–folicanthine. (i) **BA8** (10 mol%), Na_2SO_4, DCM.

Prompted by these seminal discoveries, the reactivities of 3–hydroxy–2–oxindoles have explored by a number of groups (Table 1.2). In these following studies, a broad range of nucleophiles were shown to perform well and furnish the corresponding indolyl products **130**–**137** in yields and ee values of up to 99%. The stereoselectivity obtained in all reaction examples represented in Table 1.2 were also proposed to exhibit a transition state featuring bifunctional activation.

Table 1.2: Chiral Brønsted acid–mediated reactivities of 3–hydroxyoxindoles



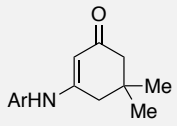
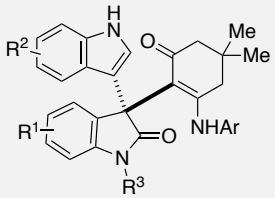
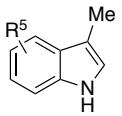
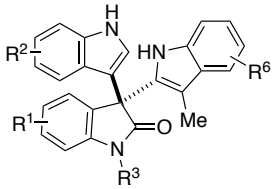
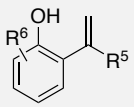
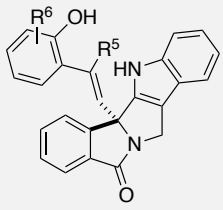
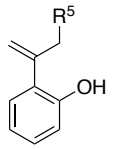
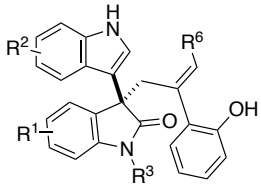
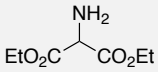
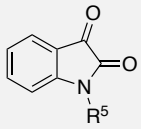
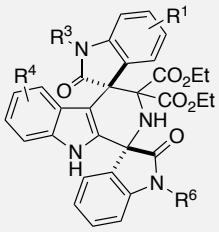
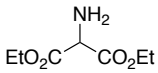
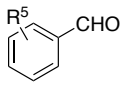
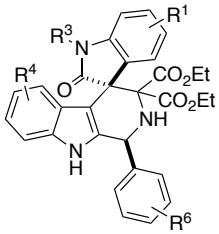
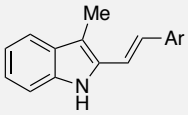
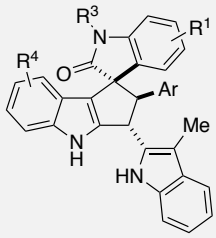
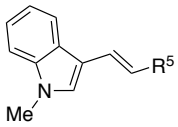
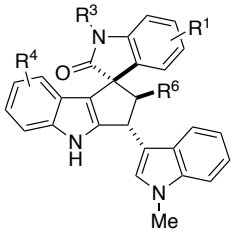
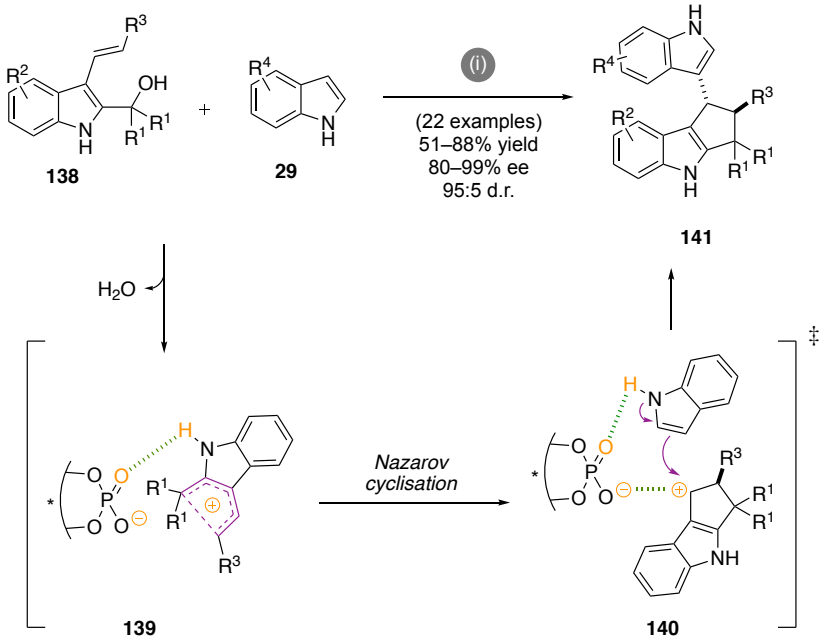
entry	reaction partner	catalyst	product	details	reference
1	 **123**	**BA4**	 **130**	24 examples 45–99% yield 74–8% ee	78
2	 **124**	**BA20**	 **131**	24 examples 84–99% yield 72–82% ee	79
3	 **88**	**BA6**	 **132**	21 examples 42–81% yield 78–94% ee	80

Table 1.2 continued

entry	reaction partner	catalyst	product	details	reference
4	 **125**	**BA30**	 **133**	25 examples 44–87% yield 86–97% ee	81
5	 **126**  **127**	**BA28**	 **134**	26 examples 40–72% yield 88–96% ee 95:5 dr	82
6	 **126**  **128**	**BA6**	 **135**	28 examples 22–60% yield 79–99% ee 33:67–74:26 dr	83
7	 **78**	**BA28**	 **136**	19 examples 72–99% yield 90–98% ee 95:5 dr	84
8	 **129**	**BA20**	 **137**	23 examples 56–93% yield 50–99% ee 75:25–95:5 dr	85

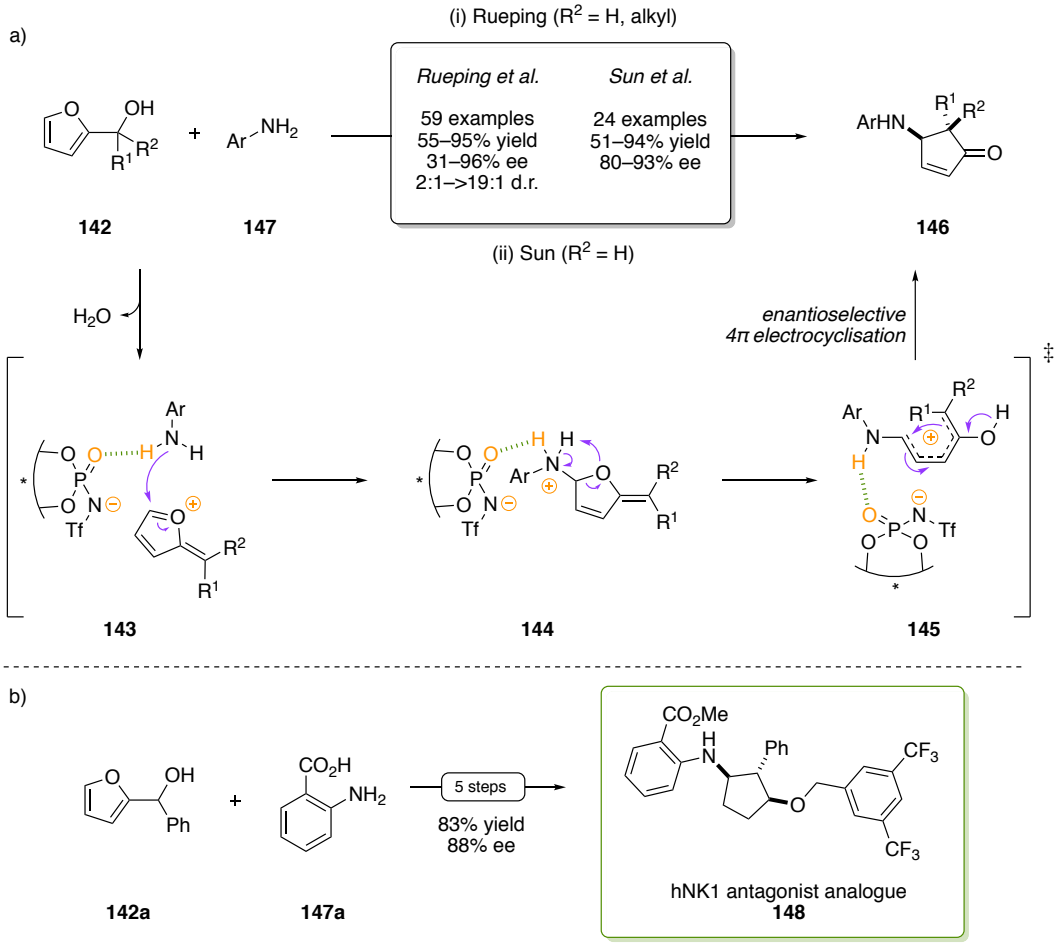
In more recent work, Shi and co–workers reported the chiral Brønsted acid–catalysed asymmetric interrupted Nazarov–type cyclisation of C3–alkenyl–substituted 2–indolylmethanols **138** with indoles **29** (Scheme 1.30).[86] Accomplished under mild reaction conditions, this gave a range of cyclopenta[*b*]indole frameworks **141** in 51–



Scheme 1.30: Brønsted acid–mediated asymmetric Nazarov–type cyclisation of C3–alkenyl–substituted 2–indolylmethanols **138** with indoles **29** to cyclopenta[*b*]indoles **141**. (i) **BA28** (10 mol%), 3 Å MS, $CHCl_3$, 25 °C.

88% yield and with 80–99% ee and ≥95:5 dr. The reaction was proposed to proceed *via* initial Brønsted acid–mediated dehydration of the alcohol substrate. The participation of the ensuing carbocationic species with the conjugate base of the catalyst to form the transition state **139** involving a contact ion pair interaction and H–bonding was proposed to occur. The chiral environment provided by these interactions was reasoned to facilitate the enantioselective Nazarov cyclisation to form the cyclic carbocation **140**. In the resultant TS, the catalyst anion was thought to form a contact ion pair with the tricyclic cation and H–bond with the indole nucleophile. It was surmised that such interactions promoted nucleophilic addition of the indole **129** to furnish the desired product in an enantio–inductive manner.

In 2016, the research groups of Rueping and Sun, independently, recognised the potential of 2–furanols **142** as pro–electrophiles that can undergo *aza*–Piancatelli rearrangement with aryl amines **147** (Scheme 1.31a).[87,88] In both reports, the



Scheme 1.31: a) Brønsted acid–mediated asymmetric Piancatelli rearrangement of 2–furanols **142** with aryl amines **147** to cyclopentanones **146**. (i) BA44 (5 mol%), $CHCl_3$, 5 °C, 24 h. (ii) (*S*)–BA39 (10 mol%), DCE, RT. b) Rueping's enantioselective synthesis of a cyclopentane-based hNK1 antagonist analogue **148**.

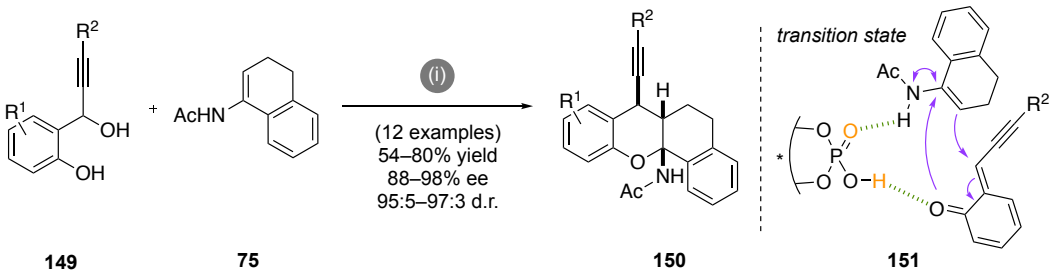
corresponding 3–aminocyclopentenones **146** were furnished in yields of up to 95% and with ee values of up to 96%. Mechanistically, the studies proposed the process to begin with the catalyst–mediated dehydration of the 2–furanol **142** to afford the chiral Brønsted acid anion–stabilised oxocarbenium intermediate and aryl amine–containing TS **143**. Nucleophilic attack by the aryl amine to the oxononium species was surmised to give the hemiaminal–containing species **144**. Its subsequent ring opening was surmised to provide the pentadienyl cationic species–containing TS **145**. Intimate electrostatic interactions between the asymmetric Brønsted acid anion and this carbocationic intermediate was reasoned to facilitate the enantioselective 4π–

electrocyclic ring closure to furnish the desired chiral cyclopentenone adduct **146**. Rueping and co–workers also demonstrated the synthetic utility of this protocol with the synthesis of the human NK1 inhibitor **148**, in an overall yield of 83% and with 88% ee over three steps from the Piancatelli rearrangement of **142a** (Scheme 1.31b).

1.2.4 Propargyl Alcohols

The reactivities of them propargyl alcohol substrate class has been mainly focussed on the functionalisation of the *sp*–hybridised carbon–carbon triple bond moiety and the nucleophilic substitution of the hydroxyl group. In general, these transformations were reported to be achieved by employing transition metal–catalysed protocols.[89–95] Synthetic examples that are promoted by organocatalytic methods, by contrast, have remained rare.

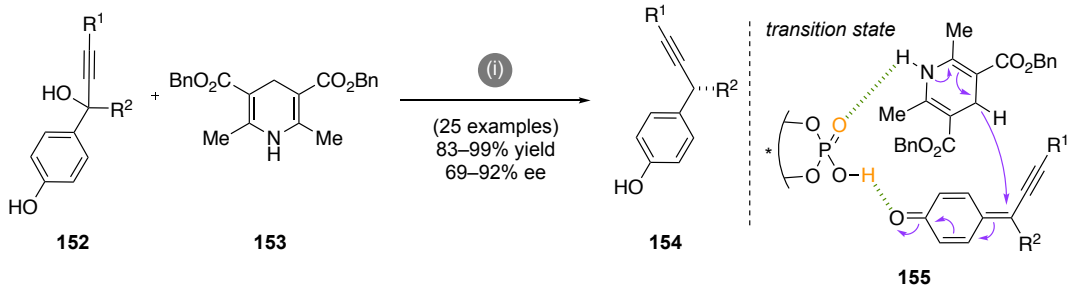
The Schneider group described one of the earliest examples, reporting the chiral phosphoric acid–catalysed substitution of the 1–(*o*–hydroxyphenyl)propargylic alcohols **149** with enamides **75** (Scheme 1.32).[96] The method furnished, amongst other heterocycles, an array of benzo[*c*]xanthenes **150** featuring three adjacent stereogenic centres in 54–80% yield and with 88–98% ee and up to 97:3 dr. In this work, the *in situ* generated *o*–QM intermediate was proposed to serve as a directing group to facilitate the conjugate addition of the enamides as in the transition state **151**.



Scheme 1.32: Brønsted acid–mediated nucleophilic substitution of alcohols 149 with enamides 75 to benzo[*c*]xanthenes 150. (i) BA7 (5 mol%), DCM, RT.

A series of control experiments supported this hypothesis as either the absence or protection of the *o*–hydroxy group was shown to result in no reaction.

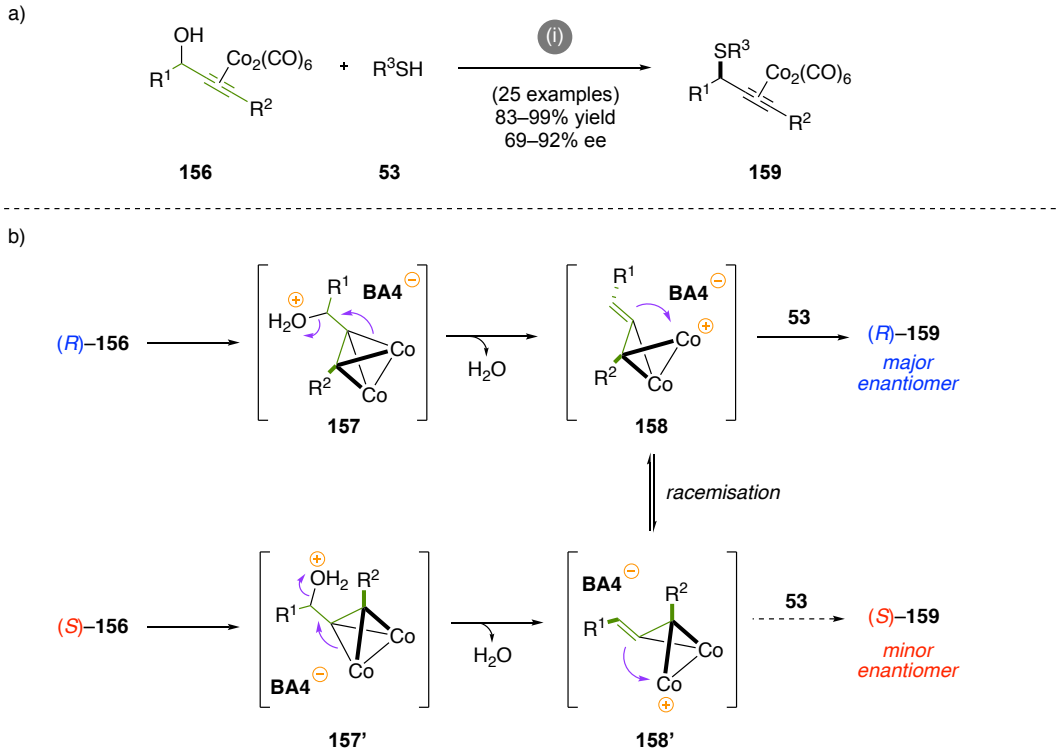
A later report by Sun and co–workers delineated the chiral Brønsted acid–mediated asymmetric reduction of propargylic alcohols **152** with the benzyl–substituted Hantzsch ester **53** (Scheme 1.33).[97] This method generated the corresponding chiral diarylmethyl alkynes **154** in 83–99% yield and with 69–92% ee. A set of control experiments demonstrated the *o*–QM intermediate was generated from the alcohol substrate upon exposure to the Brønsted acid catalyst. Subsequent addition of the hydride source was thought to result in the rapid formation of the desired enantioenriched reduction product **154**. During the optimisation of the reaction conditions, it was found that the addition of a boronic acid additive greatly improved product yield. Curiously, this was not the case when the reagents were added sequentially. This led to the deduction that the initial Brønsted acid–catalysed dehydration of the alcohol substrate was being hindered as a result of catalyst deactivation by the formation of the pyridine by–product. Thus, the addition of the boronic acid additive was to facilitate catalyst turnover by protonation of the catalyst anion. Mechanistically, it was postulated that Brønsted acid–catalysed dehydration of



Scheme 1.33: Brønsted acid–mediated asymmetric reduction of propargylic alcohols **152** with benzyl–substituted Hantzsch ester **153** to chiral diarylmethyl alkynes **154**. (i) (*S*)–**BA24** (10 mol%), 4 A MS, DCM, 38 °C, 12 h.

the alcohol substrate gave the *o*–QM intermediate which interacts with the catalyst and the Hantzsch pyridine to form the intimate transition state **155**. Transfer of the hydride anion in this TS was described to afford the desired chiral alkyne **154**.

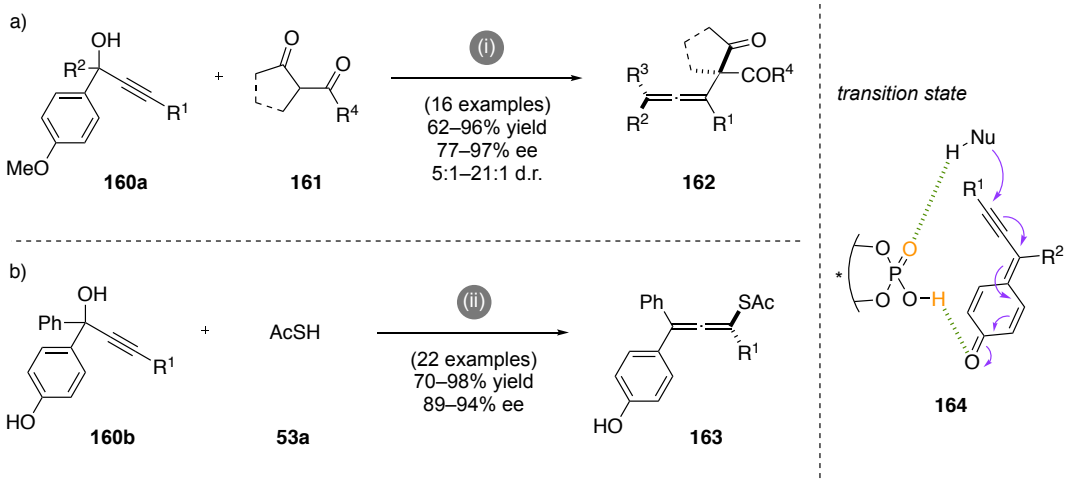
In subsequent work, the Terada group reported the chiral Brønsted acid–catalysed enantioconvergent nucleophilic substitution reaction of alkyne–dicobalt complexes **156** with thiols **53** (Scheme 1.34).[98] An expedient route for the transformation of both enantiomers of the racemic alcohol **156** was reported to afford a range of enantioenriched thioethers in 83–99% yield and with 69–92% ee. During the course of the study, the reactivities and enantioselectivities of reactions with enantioenriched and racemic starting materials was found to follow the order of (*R*)–**156** > (±)–**156** > (*S*)–**156**, to give (*R*)–**159** as the major product in all cases. It was also showed that both



Scheme 1.34: Brønsted acid–mediated nucleophilic substitution reaction of alkyne–dicobalt complexes **156** with thiols **53** to chiral propargyl thiol–dicobalt complexes **159**. (i) **BA4** (5 mol%), 4 Å MS, cyclohexane, RT.

concentration, temperature, and the number of equivalents of the thiol greatly influenced product selectivity. A lower concentration suppressed nucleophilic addition of the thiol which allowed racemisation to predominate and the effects of the asymmetric Brønsted acid catalyst to efficiently remove the disfavoured intermediate **158'**. Likewise, an increase in the number of equivalents of the thiol was shown to accelerate nucleophilic addition which favoured the retention of stereochemical information. Experimental results also revealed that an increase in temperature strongly favoured the racemisation process. This led to the proposal that the generation of the cationic intermediate takes place under the control of the chiral conjugate base of the Brønsted acid catalyst. As a consequence, its racemisation to the favoured (*R*)–**158** which can then undergo C–S bond formation to furnish the enantioenriched product (*R*)–**159**.

At about the same time, the Sun group described the Brønsted acid–mediated asymmetric synthesis of tetrasubstituted allenes **162** and **163** (Scheme 1.35).[99] In contrast to previous studies focussed on delivering carbon–centre chirality, this



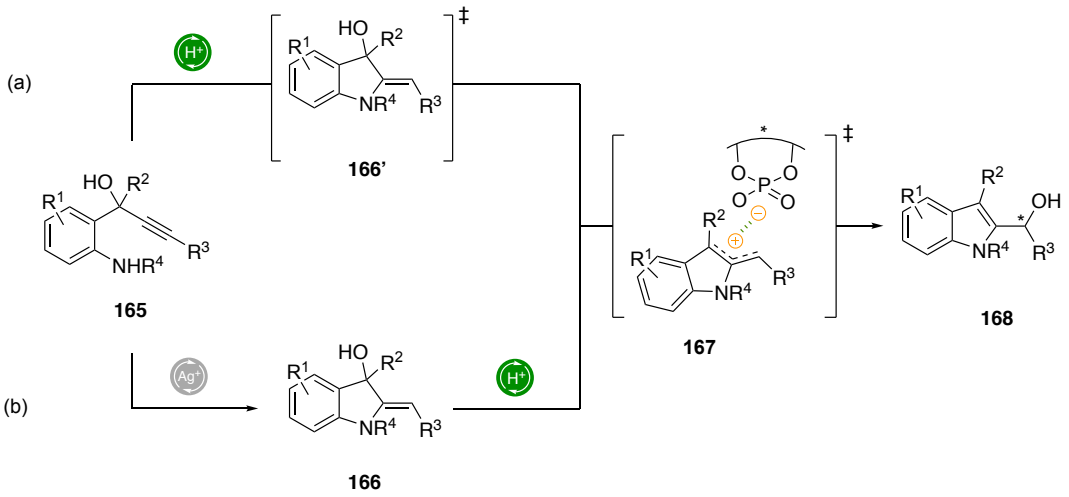
Scheme 1.35: Brønsted acid–mediated synthesis of asymmetric synthesis tetrasubstituted allenes **162** and **163**. (i) **BA27** (5 mol%), CCl_4, 0 °C or –20 °C. (ii) (*S*)–**BA42** (5 mol%), toluene or DCM, 3 Å MS, –5 °C.

manner, the ability of the propargyl alcohol to undergo C–C and C–S bond formation with **161** and **53a** to give the corresponding chiral allenes in up to 98% yield and with 98% ee and 21:1 dr was observed. The stereoinduction was postulated to result from the formation of the transition state **164** in which the chiral catalyst was H–bonding to the *p*–QM intermediate and the nucleophile to generate a chiral environment for the 1,2–conjugate addition to occur.

1.3 Proposed Work

The studies presented in this thesis will centre on the discovery and development of new synthetic methods that can rapidly and enantioselectively increase molecular complexity from alcohol pro–electrophiles driven by chiral Brønsted acid catalysis. This will be accomplished by investigating the enantioselective nature of chiral Brønsted acid catalysts with achiral alcohol substrates under mild and operationally straightforward reaction conditions.

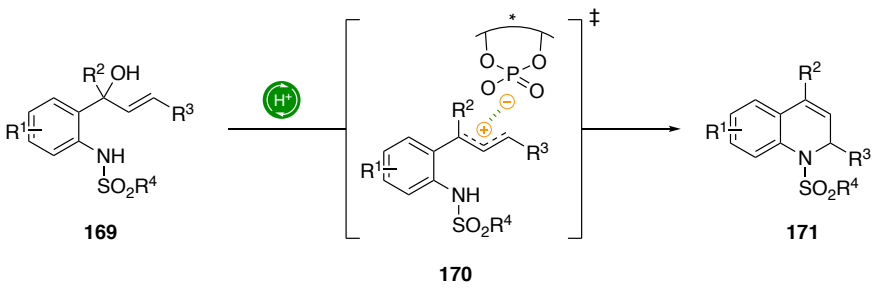
In Chapter 2 of this thesis, we propose to develop cycloisomerisation chemistry of propargyl alcohols **165** as an expedient route to 2–indolyl methanols **168** (Scheme 1.36). In previous work by the Chan group, these propargyl alcohols were shown to undergo a Brønsted acid–mediated hydroamination/1,3–AAI cascade pathway to this member of the indole family.[100] By providing the proposed carbocationic species, reasoned to be involved in the transformation, with an intimate chiral environment due to the presence of a chiral Brønsted acid, a subsequent enantioselective 1,3–AAI of the ensuing TS **167** to give the indole product might be realised (Scheme 1.36a). In the event of an asymmetric hydroamination/1,3–AAI cascade being unfeasible, it was also envisioned that a route involving the preformed Ag(I)–catalysed indolinol **166**



Scheme 1.36: Proposed synthetic route towards 2–indolyl methanols **168** from 1–(2–aminoaryl)–1,3–diphenylprop–2–yn–1–ols **165**.

undergoing the desired asymmetric 1,3–AAI *via* TS **167** would provide an alternative strategy for enantioselective 2–indolyl methanol synthesis. (Scheme 1.36b).

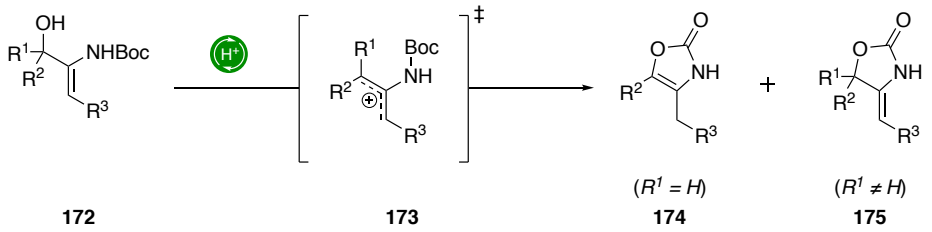
In Chapter 3 of this thesis, we will aim to develop the synthesis of 1,2–dihydroquinolines **171** *via* Brønsted acid–mediated allylic amination of 1–(2–aminoaryl)prop–2–en–1–ols **169** (Scheme 1.37). This work will first explore the ability of this substrate class to undergo Brønsted acid–catalysed dehydration to form the proposed carbocationic intermediate **170** which, upon the cyclisation step, will provide the racemic *N*–heterocyclic product **171**. The proposed transient motif could also hold the potential to form an intimate transition state with a chiral Brønsted acid



Scheme 1.37: Proposed synthetic route towards 1,2–dihydroquinolines **171** from 1–(2–aminoaryl)prop–2–en–1–ols **169**.

anion through a combination of H–bonding and counteranion interactions in order to transfer stereochemical information in the ensuing ring–forming hydroamination step to afford the enantioenriched quinoline product.

In Chapter 4 of this thesis, our aim was to realise the synthesis of oxazol–2(3*H*)–ones **174** and 5–alkenyloxazolidin–2–ones **175** from Brønsted acid–mediated cyclisation of *N*–Boc amino alcohols **172** (Scheme 1.38). This study will investigate the potential for these *β*–amino alcohols to form an allylic carbocation upon acid–catalysed dehydration in combination with the propensity of the *t*–butoxycarbonyl group to decompose under such reaction conditions. In doing so, it was envisioned that the trapping of the newly generated carbocationic intermediate motif by the carbonyl functional group in the resulting carbamic acid intermediate **173** would result in cyclisation to provide a wide range of the two *O*,*N*–heterocyclic compounds.



Scheme 1.38: Proposed synthetic route towards 2–oxazolidinones **174** and **175** from *N*–Boc *β*–amino alcohols **172**.

Chapter 2

2.0 Towards the Realisation of a Chiral Brønsted Acid–Catalysed Enantioselective 1,3–Allylic Alcohol Isomerisation of 3–Indolinols to 2–Indolyl Methanols

2.1 Introduction

Heterocyclic molecules are of considerable importance in the arsenal of the organic chemist, both as targets and as facilitators.[101,102] They are a prominent structural feature in many of the products used in our daily lives such as antioxidant, sanitiser, dye, agricultural, and pharmaceutical products.[103–109] Of the nitrogen–based heterocyclic scaffolds, the indole ring system is one of the most wide spread and versatile found in the natural world. A key component in a wide variety of biologically active natural products and building blocks in functionalised materials,[110] indole is a portmanteau derived from the constituents from which it was first isolated, *ind*igo dye and *ole*ium.

The indole family possess the unique ability to structurally mimic peptides and reversibly bind, with high affinity, to a multitude of receptors.[111–114] Their ability to bind reversibly to an array of enzymes has been powerful motivation for synthetic chemists to discover original modes of action and novel structures of value. In the human body, the proficiency to bind reversibly to receptors has earned this *N*–heterocycle membership to an association of compounds introduced by Evans *et al*. known as "privileged scaffolds".[115] For example, the indole–containing biomolecules melatonin, serotonin, and tryptophan have been shown to regulate the sleep–wake cycle, contribute to the formation of neurons, and feature as an amino acid building block in various proteins, respectively (Figure 2.1a).[116,117]

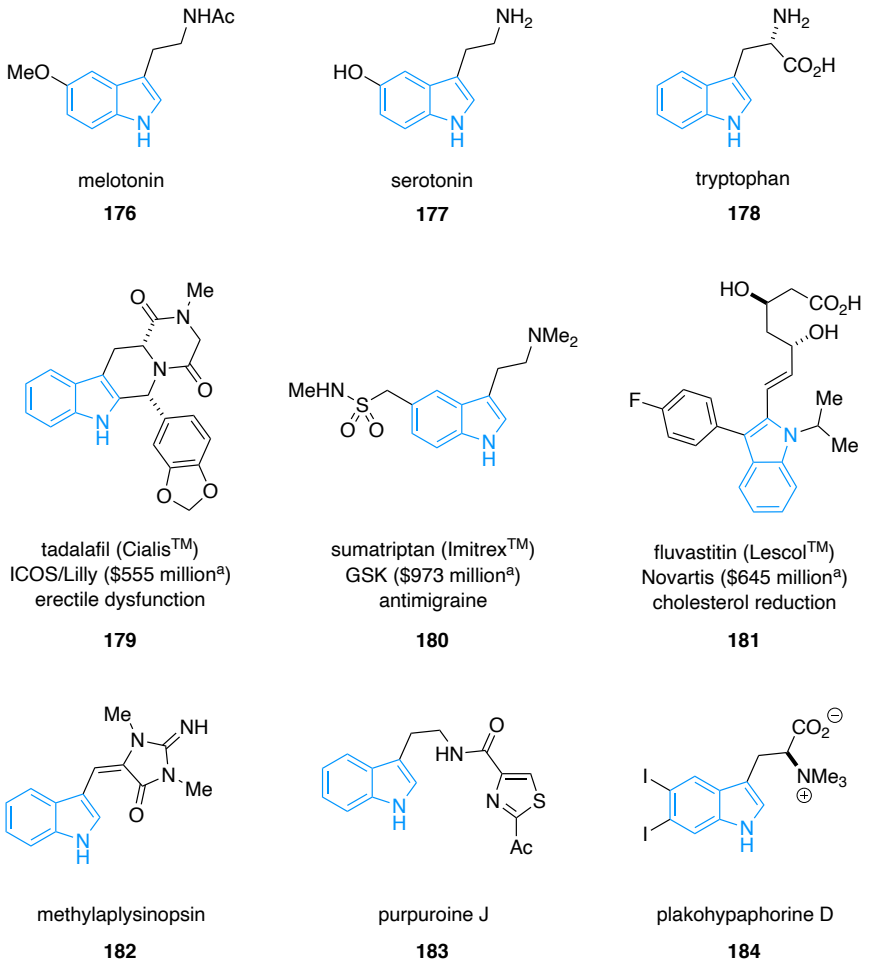


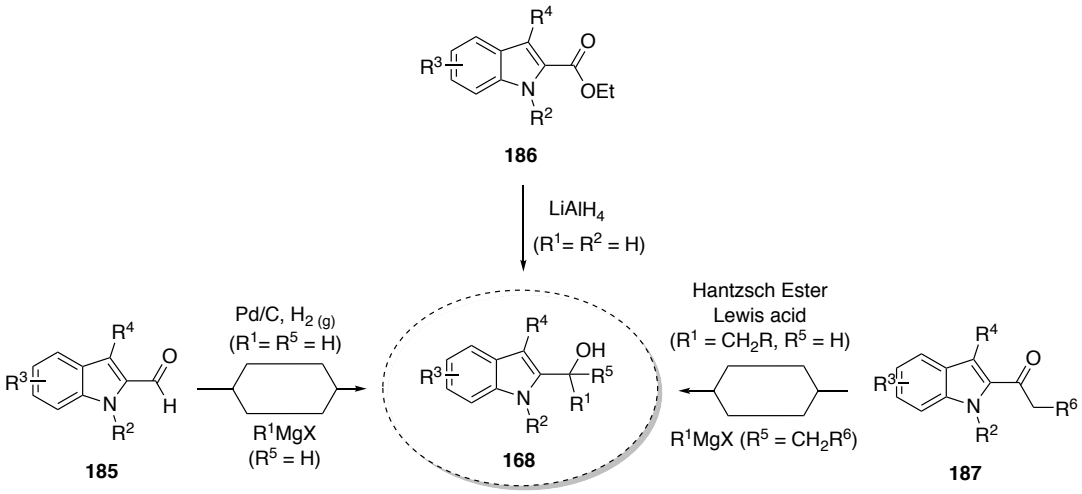
Figure 2.1: a) Selected indole derivatives featured in animal biology. b) Selected pharmaceuticals containing the indole core structure. [a]US sales in 2008.[109] c) Marine alkaloids containing the indole structure.

A wide variety of naturally occurring and synthetic compounds containing the *N*–heterocycle have been found to exhibit a plethora of bioactivities such as antifungal, anticancer, antihypertensive, antiHIV, and antidiabetic activity.[110] In the pharmaceutical industry, leading examples include taladafil **179** developed by ICOS/Lilly for the treatment of erectile dysfunction, sumatriptan **180** from GSK for the treatment of migraines, and fluvastatin **181** from Novartis for the treatment of high cholesterol (Figure 2.1b).[110,118–126]

In the natural world, an increasing number of indole alkaloids isolated from a variety of marine organisms have been reported to have similar structures to that of human

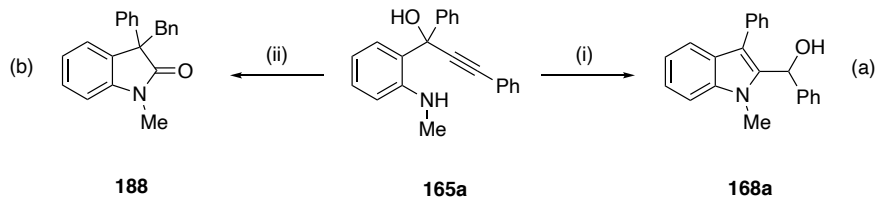
neurotransmitter compounds. As a consequence, it is postulated that many of these marine alkaloids may also possess or have hitherto unrealised neurological activity.[119,127,128] For instance, the marine indole alkaloid methylaplysinopsin **182** inhibits monoamine oxidase (Figure 2.1c).[129] In addition, the alkaloids purpuroine J **183** and plakohypaphorine D **184** have been shown to display significant antihistaminic activity.[130]

For these reasons, the design, synthesis, and modification of indoles has and continues to be an actively pursued area of chemistry.[102,131–136] While this has led to the development of a myriad of methods for indole synthesis over the years, little attention has been paid to the generation of 2–indolyl methanols. To our knowledge, there are also no examples for synthesis of the *N*–heterocycle featuring an asymmetric 1,3–allylic alcohol isomerisation (1,3–AAI) strategy. Currently, synthetic methods available to access this member of the indole family have relied on Grignard reaction and reduction of 2–carbonyl–substituted indoles to give the corresponding secondary or tertiary alcohols (Scheme 2.1).[137–143]



Scheme 2.1: Reported methods to generate indolyl methanols.

Current synthetic methods that realise 1,3–AAIs have been limited to racemic methods, asymmetric transformations mediated by lipases, and Rh–oxo–catalysis with enantioenriched starting materials.[144–147] An asymmetric catalytic 1,3–AAI leading to the enantioselective synthesis of indolyl methanols has remained unexplored. In this context, we were drawn to the potential cycloisomerisation chemistry of *o*–anilinyl–tethered propargyl alcohols **165a** (Scheme 2.2). In previous work, the substrate class was serendipitously discovered to undergo silica–gel–catalysed cycloisomerisation to give the corresponding 2–oxindoles **188** in 91% yield (Scheme 2.2a).[100] The mildly acidic nature of SiO_2 was responsible for the proposed hydroamination/semi–pinacol rearrangement of the propargyl alcohol. This process was likely initiated with SiO_2 activation of the alkyne moiety followed by a nucleophilic attack of the alkylamido group. Migration of the hydroxyl group, and subsequent oxidative 1,2–migration of the benzyl group from the C-2 to the C-3 position, then affords the oxindole **188**. When the stronger Brønsted acid *p*–TsOH was employed, however, a different cycloisomerisation pathway was shown to occur to afford the (1*H*–indol–2–yl)methanol **168a** in 38% yield (Scheme 2.2b). One possible hypothesis for this latter process was the formation of an allylic cation resulting from a Brønsted acid–catalysed hydroamination/1,3–AAI cascade pathway.



188 **165a** **168a**

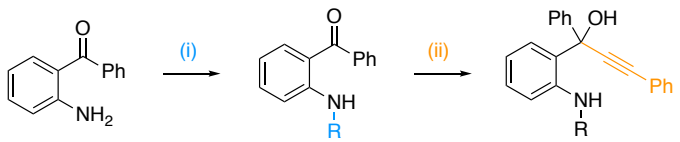
Scheme 2.2: Reported synthesis of 2–oxindoles and indolyl methanols from 1–(2–aminoaryl)–1,3–diphenylprop–2–yn–1–ols. i) *p*–TsOH (5 mol%), *n*–hexane/EtOAc (20:1 v/v), RT, 38% yield. ii) SiO_2 (100 eq.), *n*–hexane/EtOAc (20:1 v/v), RT, 91% yield.

With this in mind, we anticipated an asymmetric version of this functional group transformation could be accomplished through the application of chiral Brønsted acid catalysis. We envisioned the development of this approach to access 2–indolyl methanols in an asymmetric manner would be attractive in view of their potential applications in the agricultural, pharmaceutical, and materials–based industry, and as building blocks in organic synthesis.

2.2 Results and Discussion

2.2.1 Synthesis of the Starting Material

All *N*–protected 1–(2–aminoaryl)–1,3–diphenylprop–2–yn–1–ols **165** examined in the present work were prepared from the corresponding 2–aminoacetophenones **189** in two steps following known procedures (Scheme 2.3).[100,148] The synthesis of propargyl alcohols **165** involved an initial amination of **189** with either methyl iodide or tosyl chloride under basic conditions to afford *o*–aniline derivatives **190a** and **190b** in 48 and 66% yield, respectively. Methylation of **189** under the described conditions afforded 21% yield of the dimethylation product that was easily separated employing column chromatography on silica–gel. For both compounds **190a** and **190b**, subsequent LDA–mediated propargylation with phenylacetylene provided access to the desired propargyl alcohol **165a** and **165b** in respective yields of 76 and 99%.

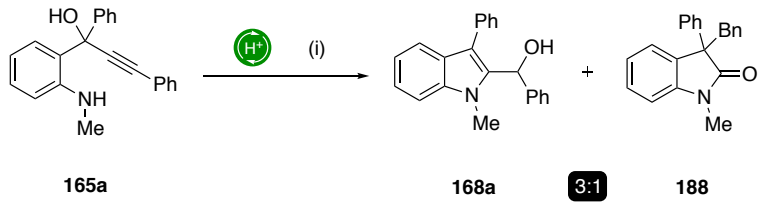


189 | **190a** (R = Me), **190b** (R = Ts) | **165a** (R = Me), **165b** (R = Ts)

Scheme 2.3: Synthesis of propargyl alcohols **165** from 2–aminoacetophenones **189**. i) R = Me: MeI, K_2CO_3, 80 °C, DMF, 48%. R = Ts: TsCl, pyridine, 66% yield. ii) R = Me: phenylacetylene, LDA, –78 °C to RT, THF, 99% yield (R = Me), 76% yield (R = Ts).

2.2.2 Chiral Brønsted Acid–Mediated Enantioselective Hydroamination/1,3–AAI of *o*–Anilinyl–Substituted Propargyl Alcohols

Our studies began by examining the chiral Brønsted acid–catalysed cyclisations of propargyl alcohol **165a**, which was initially chosen as the model substrate to establish the optimum reaction conditions. To confirm the reproducibility of the reported Brønsted acid–mediated rearrangement to give propargyl alcohol **165a**, the reaction of the substrate in a solution of *n*–hexane and EtOAc (20:1) with 10 mol% of *p*–TsOH as the catalyst was first examined (Scheme 2.4).[100]



Scheme 2.4: Initially attempted *p*–TsOH–catalysed cyclisation of 165a to indolyl methanol 168a. i) *p*–TsOH (10 mol%), *n*–hexane/EtOAc (20:1), 75% yield of 168a, 25% yield of 188.

Under these reaction conditions, it was found that a separable mixture of the desired indolyl methanol **168a** and 2–oxindole **188** was generated in a ratio of 3:1 and respective yields of 75 and 25%. Recrystallisation of a sample of **168a** allowed access to a single crystal suitable for the determination of its crystal structure by X–ray crystallography (Figure 2.2).

An enantioselective version of the desired 5–*endo*–*dig*–type cyclisation was next explored, and the reaction conditions initially investigated are summarised in Table 2.1. Chiral Brønsted acid catalyst **BA1** was employed for all control experiments discussed in Table 2.1 where the effect of various solvents, reaction temperatures, and the inclusion or exclusion of 4 Å MS was examined. The chiral phosphoric acid was

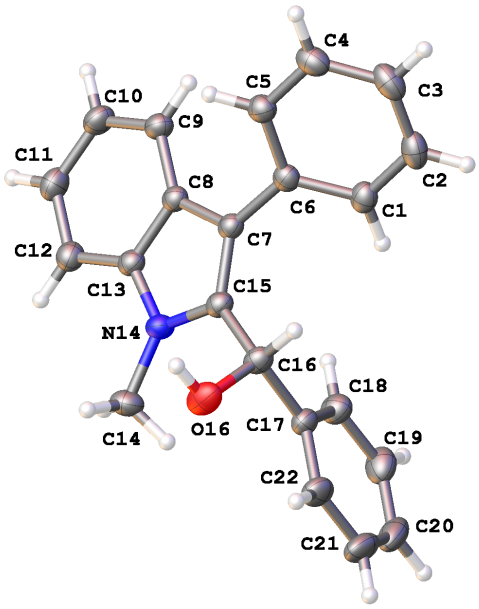
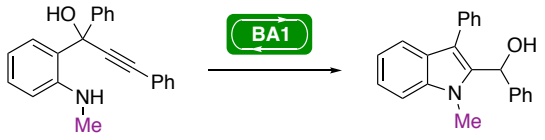


Figure 2.2: ORTEP drawing of *N*–(2–benzoylphenyl)–4–methylbenzenesulfonamide **168a** with thermal ellipsoids at 50% probability levels.

selected due to its commercial availability and the possibility to readily modify the structure in further studies directed at establishing the reaction conditions to obtain optimum product enantioselectivity.

In the first instance, the transformation of **165a** to **168a** was examined on a 0.1 mmol scale in anhydrous THF (1 mL) and with 50 mg of 4Å MS at room temperature (entry 1). These reaction conditions produced **168a** in 23% yield after 96 h. Similarly, repeating the reaction conditions with toluene instead of THF as the solvent resulted in a long reaction time of 86 h and a low product yield of 35% (entry 2). An examination of the reaction conditions without the exclusion of air or moisture demonstrated the transformation in THF at room temperature for 0.5 h to be robust, achieving a product yield of 80% (entry 3). Conversion of propargyl alcohol **165a** to the desired indolyl methanol product **168a** in 92% yield was also achieved by employing toluene as the solvent at room temperature for 0.25 h (entry 4). The analogous control experiment at 0 °C for 1 h led to a product yield of 92% (entry 5).

Table 2.1: Summary of the initial screening of conditions of the Brønsted acid–catalysed cyclisation of **165a** to **168a**.



165a **168a**

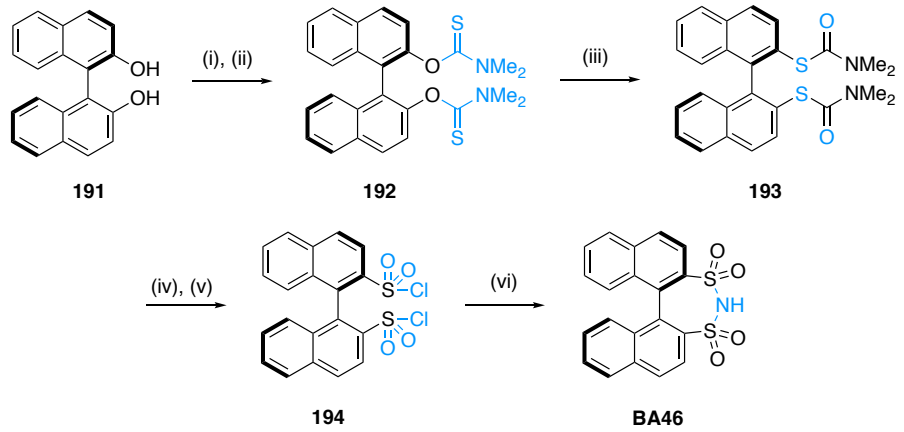
entry[a]	solvent	4Å MS (mg)	time (h)	temp. (°C)	yield (%)[b]	ee (%)[c]
1[d]	THF	50	96	RT	23	0
2[d]	PhMe	50	84	RT	35	0
3	THF	0	0.5	RT	80	0
4	PhMe	0	0.25	RT	92	0
5	PhMe	0	1	0	92	0
6	PhMe	0	24	–78	17	0

[a]All reactions were conducted on a 0.1 mmol scale in solvent (1 mL) with catalyst (10 mol%) without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.
[d]Reaction conducted using anhydrous solvent and an N_2 atmosphere.

At –78 °C, however, poor reactivity towards the cycloisomerisation of **165a** to **168a** was observed after 24 h, with the cyclic product obtained in 17% yield (entry 6). Moreover, in all the reaction conditions examined in Table 2.1, no chiral induction was detected by HPLC analysis, with the product furnished as a racemate in each instance.

In view of these initial findings, the BINOL–based disulfonimide acid catalyst **BA46** (BINBAM) was examined.[149] This is a chiral acid catalyst of interest due the amino group being buried more deeply in the chiral pocket than in the equivalent phosphoric acid. The synthetic route employed to access this scaffold is described in Scheme 2.5. This involved initial generation of the bis(*O*–arylthiocarbamate) **192** in 60% yield under basic conditions from enantiopure and commercially available (*R*)–BINOL **191**.

The desired 2,2'–disulphur centres were then installed by thermally induced Newman–Qwart rearrangement to afford the bis–(*S*–arylthiocarbamate) **193** in 59% yield. Subsequent oxidative cleavage to the bis–sulfonic acid followed by NCS–mediated activation afforded the disulfonyl chloride **194** in 51% yield. Passing gaseous ammonia through a solution of **194** suspended in benzene promoted the final cyclisation which was then acidified after purification to afford the target Brønsted acid **BA46** in 60% yield over six steps.

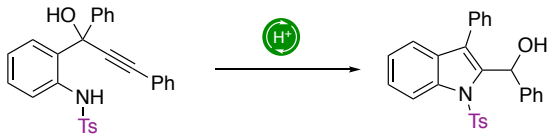


Scheme 2.5: Synthetic route to the BINBAM acid catalyst BA46.[150] i) NaH, DMF. ii) ClC(C=S)NMe_2, 85 °C, 4 h, 60% yield. iii) Microwave (300 Watt), 200 °C, 20 min, 59% yield. iv) H_2O_2/HCO_2H, DCM, then HCl. v) NCS, HCl(aq), MeCN, 15 °C, 15 min, 51% yield. vi) NH_3(g), C_6H_6, RT, 2 h, 68% yield.

In tandem with a change of catalyst, attention was turned to the *N*–Ts propargyl alcohol substrate **165b** (Table 2.2). It was reasoned that a substrate bearing a nitrogen centre that was less nucleophilic in character might contribute to the induction of product selectivity. This was based on the working hypothesis that a less reactive amine group might allow for the formation of a more intimate transition state between it and the chiral Brønsted acid through hydrogen–bonding interactions prior to the hydroamination step. However, we discovered that neither *p*–TsOH, **BA1** (pK_a = 3.4, DMSO),[25] nor the more acidic BINBAM catalyst **BA46** (pK_a = 0.2, DMSO)[25] were able to catalyse the cycloisomerisation of **165b** to **168b** (Table 2.2). In all three

experiments that were conducted in toluene at room temperature, ^{1}H NMR analysis confirmed only the substrate **165b** present in the crude reaction mixtures. Presumably, our attempts to promote strong hydrogen–bonding interactions by fine–tuning the nucleophilicity of the substrate may have unintentionally supressed its ability to undergo hydroamination.

Table 2.2: Summary of the screening of conditions for the Brønsted acid–catalysed cyclisation to **168b**.



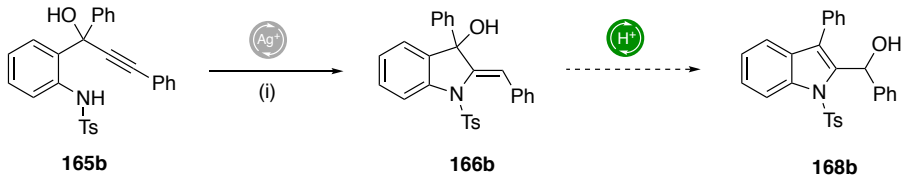
165b **168b**

entry[a]	catalyst	yield (%)[b]
1	*p*–TsOH	–[c]
2	**BA1**	–[c]
3	**BA46**	–[c]

[a]All reactions were conducted on a 0.1 mmol scale in PhMe (1 mL) with catalyst (10 mol%) for 24 h without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]No reaction based on ^{1}H NMR analysis of the crude reaction mixture.

2.2.3 Chiral Brønsted Acid–Mediated Enantioselective 1,3–AAI of 3–Indolinols

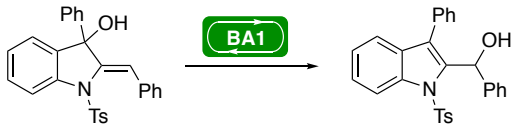
Concluding that the development of the chiral Brønsted acid–mediated hydroamination/1,3–AAI of **165b** may not be achievable, we queried whether an asymmetric rearrangement of a preformed 3–indolinol to **168b** might be a more viable strategy (Scheme 2.6). With this is mind, AgOAc–catalysed intramolecular amination of the sulphonamide **165b** and subsequent protodemetalation afforded the indolinol product **166b** in 99% yield.[148]



Scheme 2.6: Synthetic route towards 2–indolyl methanol **168b** in a step–wise method *via* indolinol **166b**. i) AgOAc (5 mol%), MeCN, RT, 1 h, 99% yield.

With the substrate in hand, its reactivity in the presence of the chiral phosphoric acid **BA1** was examined and the results are summarised in Table 2.3. Initially, the transformation of **166b** to **168b** was examined at the 0.1 mmol scale at room temperature with toluene as the reaction solvent and 10 mol% of the catalyst at room temperature (entry 1). These conditions produced a product yield of >99% and an ee value of 8% over 12 h. At this stage in experimentation, a single crystal of **168b** of suitable quality for X–ray analysis was produced to allow its structure to be determined (Figure 2.3).

Table 2.3: Summary of the screening of conditions for the Brønsted acid–catalysed 1,3–AAI of **166b**.



entry[a]	catalyst loading (mol%)	time (h)	temp (°C)	yield (%)[b]	ee (%)[c]
1	10	12	RT	>99	8
2	5	18	RT	>99	8
3	5	1	50	>99	8
4	1	20	RT	>99	9

[a]All reactions were conducted on a 0.1 mmol scale in PhMe (1 mL) at RT without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

Next, examining the reaction with 5 mol% of catalyst **BA1** resulted in a reaction time of 18 h and a product yield and ee value of >99% and 8%, respectively (entry 2).

Similarly, repeating the reaction at an elevated temperature of 50 °C achieved a product yield of >99% and an ee value of 8% after 1h (entry 3). At room temperature, the cycloisomerisation of **166b** to **168b** at a catalyst loading of 1 mol% achieved a comparable product yield of >99% and 9% ee after 20 h (entry 4).

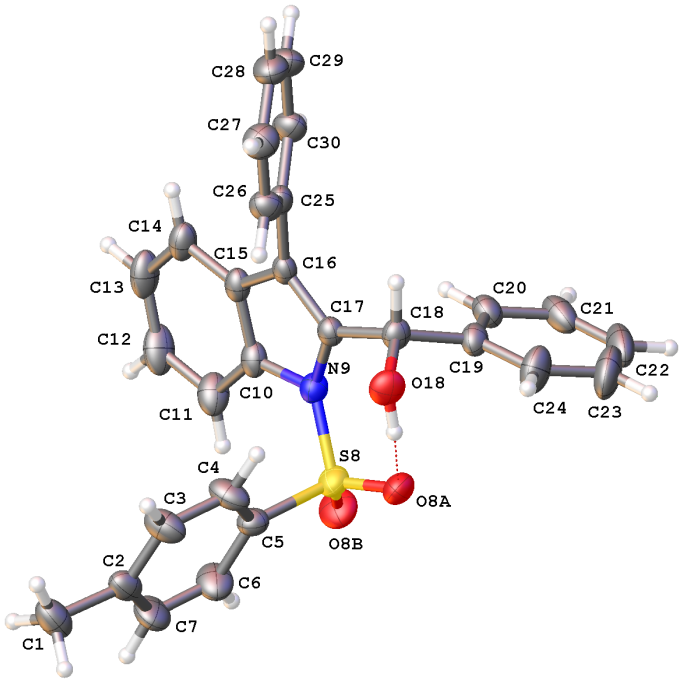
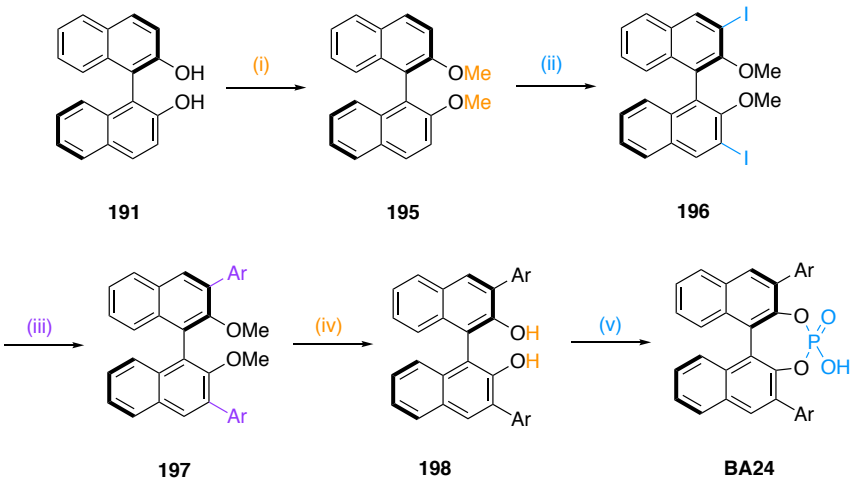


Figure 2.3: ORTEP drawing of phenyl(3–phenyl–1–tosyl–1*H*–indol–2–yl)methanol **168b** with thermal ellipsoids at 50% probability levels.

2.2.4 Synthesis and Evaluation of Sterically Encumbered Chiral Phosphoric Acid Catalysts

Encouraged by the moderate stereoinduction observed by the **BA1**–catalysed 1,3–AAI of **166b**, efforts were channelled toward the synthesis of BINOL–based chiral phosphoric acids featuring bulky aryl substituents at the 3 and 3' positions. In view of the many reported chiral transformations employing the TRIP–substituted Brønsted acid **BA24**, this was structure to be our first port of call (Scheme 2.7).[20,151,152] The synthetic route employed giving access to the chiral Brønsted acid over five steps



Scheme 2.7: i) MeI, K_2CO_3, acetone, RT, 99% yield; ii) I_2, THF, *n*–BuLi, TMEDA, –78 °C–RT, 54% yield; iii) 2,4,6–triisopropylphenylmagnesium bromide, $Ni(PPh_3)_2Cl_2$, Et_2O, 0 °C–RT, 24% yield; iv) BBr_3, DCM, 99% yield; v) Pyridine, then $POCl_3$, then H_2O, RT–reflux, 68% yield. Ar = 2,4,6–triisopropylphenyl.

involved the initial protection of the commercially available and optically pure (*R*)–BINOL **191**.[153] In the presence of methyl iodide under basic conditions, this afforded the desired dimethoxy scaffold **195** in 99% yield. Subsequent methoxy–directed *ortho*–lithiation–halogenation generated the diiodo adduct **196** in 54% yield. This laid the path for the application of Ni–mediated cross–coupling chemistry with the appropriate Grignard coupling partner to achieve the installation of the desired 3,3'–aryl substituents to afford **197** in 24% yield. Lastly, boron–mediated deprotection followed by phosphorylation with $POCl_3$ and subsequent hydrolysis afforded the target phosphoric acid catalyst **BA24** in 68% yield.

The control experiments of the indolinol **166b** with the newly acquired TRIP–substituted catalyst **BA24** was next examined and the results are summarised in Table 2.4. This revealed exposing 5 mol% of **BA24** to the substrate in toluene at room temperature required 120 h to achieve **168b** in 73% yield and 10% ee (entry 1). Likewise, repeating the reaction at a catalyst loading of 10 mol%, a similar reaction time of 138 h was needed for the complete consumption of the substrate, giving a

Table 2.4: Summary of the reaction conditions screened for the BA24–catalysed 1,3–AAI of 166b.

166b 168b

entry[a]	catalyst loading (mol%)	time (h)	yield (%)[b]	ee (%)[c]
1	5	120	73	10
2	10	138	74	10

[a]All reactions were conducted on a 0.1 mmol scale in PhMe (1 mL) at RT without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

product yield and ee value of 74 and 10%, respectively (entry 2). From these findings it can be seen that catalyst **BA24** was unable to provide a significant increase in selectivity. In response to these results, and to address the current low level of enantioselectivity obtained with **BA24**, a second set of commercially available BINOL–based chiral phosphoric acids were examined (Figure 2.4). The reactions of **166b** mediated by the newly acquired chiral phosphoric acid catalysts were investigated (Table 2.5). In the presence of 5 mol% of **BA2** in distilled toluene at room temperature for 120 h, a product yield of 5% along with an ee value of 5% was obtained (entry 1). Repeating the reaction conditions without the exclusion of air or moisture afforded similar results, with a 6% product yield and an enantiomeric excess of 7% found (entry 2). Next, examining the reaction at an elevated temperature of 50 °C for

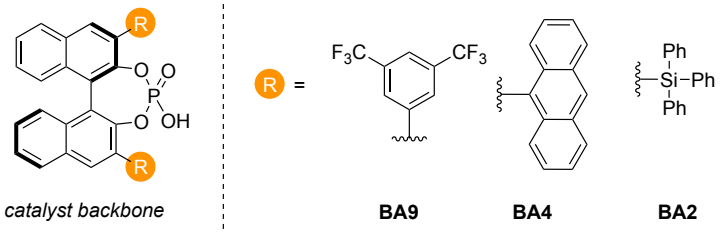
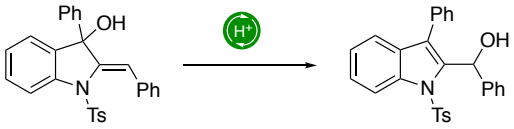


Figure 2.4: BINOL–based chiral phosphoric acids acquired for further screening.[270]

Table 2.5: Summary of the chiral acids screened for the Brønsted acid–catalysed 1,3–AAI of **166b**.



166b **168b**

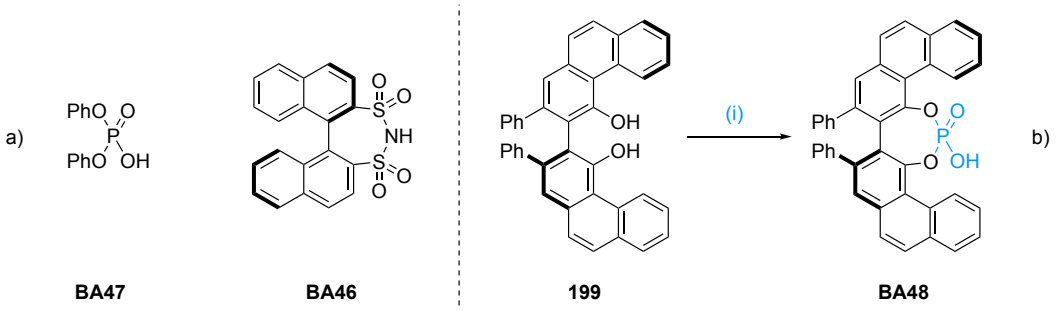
entry[a]	catalyst	temp. (°C)	time (h)	anhydrous conditions	yield (%)[b]	ee (%)[c]
1	**BA2**	RT	120	✔	5	5
2	**BA2**	RT	120	✖	6	7
3	**BA2**	50	120	✖	62	4
4	**BA9**	RT	120	✔	>99	3
5	**BA9**	RT	120	✖	>99	4
6	**BA9**	50	16	✖	>99	5
7	**BA4**	RT	120	✔	45	22
8	**BA4**	RT	120	✖	56	25
9	**BA4**	50	120	✖	97	7

[a]All reactions were conducted on a 0.1 mmol scale in PhMe (1 mL) with catalyst (5 mol%) without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

120 h afforded **168b** in 62% yield along with an ee value of 4% (entry 3). Reactions with **BA9** in place of **BA10** as the catalyst were next examined (entry 4–6). At room temperature and over 120 h, the reaction afforded the product in quantitative yield and with 3 % ee (entry 4). Repeating the reaction conditions without the use of anhydrous conditions afforded similar results over 120 h, with a >99% product yield and an ee value of 4% (entry 5). Similarly, examining the effect of an elevated reaction temperature of 50 °C after 16 h produced a comparable product yield of 79% along with 5% ee (entry 6). Experiments employing the 9–anthracenyl substituted Brønsted acid catalyst **BA4** revealed that in distilled toluene at room temperature, cycloisomerisation of **166b** gave **168b** in 45% yield and 22% ee over 120 h (entry 7). Similarly, the analogous reaction conditions without the exclusion of air and moisture achieved a product yield of 56% and 25% ee (entry 8). While repeating the experiment

at 50 °C afforded an improved product yield of 97%, a lower enantiomeric excess of 7% was observed (entry 9). The marked difference in reactivity in experiments mediated by **BA2** and **BA9** containing the electron–withdrawing $SiPh_3$ and 3,5–(trifluoromethyl)phenyl motifs, respectively, led to the conclusion that such electronic factors may not be a significant contributing factor for determining selectivity in these reactions (entry 2 versus entry 5). Likewise, the difference in reactivity found for experiments catalysed by **BA2** and **BA4**, where the steric bulk possessed by each catalyst might be considered to be relatively comparable, suggested this may also not be a significant contributor to the asymmetric outcome of the reaction (entry 2 versus entry 8). In this context, we reasoned that the shape occupied in space by the substituents at the 3 and 3' positions of the Brønsted acid should be the major consideration in further optimisation studies and not their stereoelectronic nature.

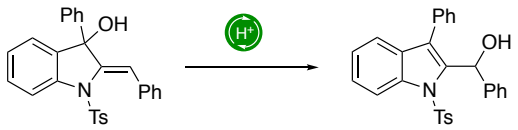
With this in mind, the reaction of **166b** with the BINBAM catalyst **BA46** and a VAPOL–based phosphoric acid **BA48** was examined (Scheme 2.8). As a comparison of reactivity, the 1,3–AAI of the substrate mediated by the achiral Brønsted acid diphenyl phosphate **BA47** was also investigated (Scheme 2.8a). Synthesis of **BA48** in 76% yield from its (*R*)–VAPOL diol **199** involved the one–pot phosphorylation with $POCl_3$ under basic conditions and hydrolysis (Scheme 2.8b).



Scheme 2.8: a) Further acids employed in future screening. b) Synthesis of B48 from corresponding diol. i) Pyridine, $POCl_3$, H_2O, RT–reflux, 76% yield.

The results obtained from the cycloisomerisation of **166b** mediated by the newly acquired chiral phosphoric acid catalysts are summarised in Table 2.6. Initially, the presence of 5 mol% of **BA48** in distilled toluene at room temperature was examined (entry 1). These conditions afforded a product yield of >99% and 20% ee over 120 h. Repeating the reaction conditions without the exclusion of air or moisture produced similar results, with a product yield and ee value of >99 and 10% being obtained (entry 2). An increase in reaction temperature to 50 °C over 16 h revealed a comparable yield and, curiously, an increased enantiomeric excess value of 14% (entry 3). Next, the reactions mediated by the BINBAM catalyst **BA46** were examined. Employing distilled toluene at room temperature over 16 h revealed a >99% product yield but with

Table 2.6: Summary of the chiral acids screened for the Brønsted acid–catalysed 1,3–AAI of 166b.



166b **168b**

entry[a]	catalyst (5 mol%)	temp. (°C)	time (h)	anhydrous conditions	yield (%)[b]	ee (%)[c]
1	**BA48**	RT	120	✔	>99	20
2	**BA48**	RT	120	✖	>99	10
3	**BA48**	50	16	✖	>99	14
4	**BA46**	RT	16	✔	>99	0
5	**BA46**	RT	16	✖	>99	6
6	**BA46**	50	16	✖	>99	0
7	**BA47**	RT	2	✔	>99	–
8	**BA47**	RT	2	✖	>99	–
9	**BA47**	50	2	✖	>99	–
10[d]	**BA47**	RT	24	✖	>99	–

[a]All reactions were conducted on a 0.1 mmol scale in PhMe (1 mL) with catalyst (5 mol%) without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.
[d]Reaction conducted with a 1 mol% catalyst loading.

no chiral induction (entry 4). Repeating the reaction conditions without the exclusion of air or moisture produced comparable yields along with 6% ee (entry 5). Increasing the reaction temperature to 50 °C was also shown to lead to a product yield of >99% but no enantioselectivity over 16 h (entry 6). This result is curious as a decrease in reaction time would have been reasonably expected (entry 5 versus entry 6).

The reactivity of the substrate toward 1,3–AAI mediated by the achiral Brønsted acid diphenyl phosphate **BA47** was next investigated. The results, summarised in entries 7–9, illustrate that employing inert or atmospheric conditions, the reaction at room temperature or 50 °C for 2 h had no significant effect on reactivity, with >99% product yield afforded in all cases. An analogous control experiment conducted with **BA47** at a catalyst loading of 1 mol% in toluene at room temperature for 24 h revealed a >99% product yield (entry 10). A catalyst loading of 1 mol% was not, however, considered reasonably feasible for the bulkier chiral Brønsted acids **BA48**, **BA46**, and **BA47** due to the likelihood for the need for extended reaction times.

A comparison of the reactivities found for the reactions of **166b** promoted by Brønsted acids **BA1**, **BA48**, **BA46**, and **BA47** under the conditions described in Table 2.3, entry 2, and Table 2.6, entries 2, 5, and 8, respectively, revealed that an increase in acidity did not lead to an increase in reactivity (Figure 2.5). It was hypothesised that an increased acidity of the Brønsted acid catalyst would result in faster hydroxyl protonation, dehydration, and subsequent formation of an allylic cation. As Brønsted acids **BA47** and **BA1** possess comparable pK_a values, a comparable level of reactivity might be expected. However, diphenyl phosphate catalyst **BA47** displays a reactivity 9–times higher than that of **BA1**. This difference in reactivity could be attributed to the steric crowding of the phosphoric acid proton in **BA1**. As noted, the acidic proton

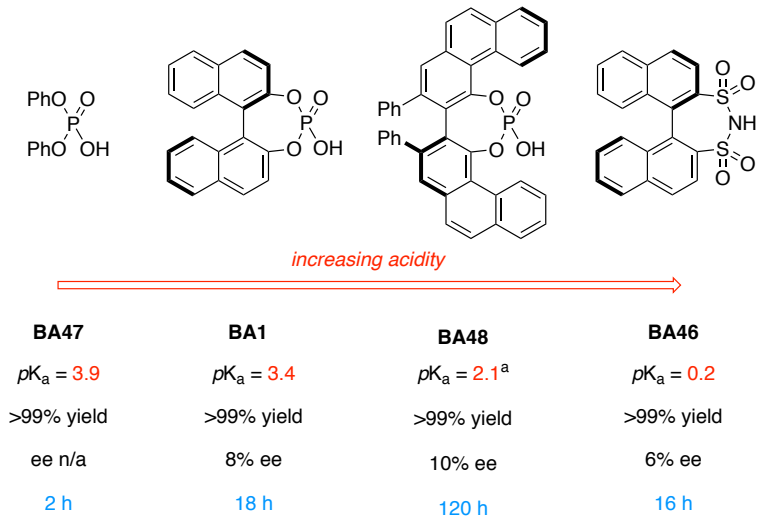
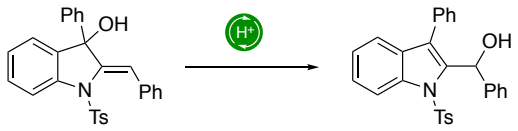


Figure 2.5: Reactivity and selectivity comparison between acids BA47, BA1, BA48, and BA46. a) Calculated pK_a value.[154]

of the disulfonimide catalyst **BA46** is reported to be more deeply buried in the chiral pocket than Brønsted acid **BA1**.[149] As a result, and despite possessing an acidity of more than 3 pK_a units lower than that of **BA1**, the disulphonamide catalyst **BA46** exhibits comparable reactivity and selectivity. This further emphasises the role of steric interactions between the catalyst and the substrate on the reactivity of the latter. This hypothesis is further supported by the more sterically encumbered Brønsted acid **BA48**. In this control experiment, a reaction time of 120 h was required to afford a comparable product yield of 99%.

With regards to reactivity and selectivity, our studies have, thus far, shown the most effective BINOL–based phosphoric acids to be the bis(trifluoromethylphenyl) and anthracenyl–substituted catalysts **BA4** and **BA9** (Table 2.5, entries 5 and 8, respectively). With this is mind, the effect of solvent on the 1,3–AAI of alcohol **166b** in conjunction with these catalysts was examined (Table 2.7). In a previous study with **BA9** as the catalyst, the most effective conditions comprised of 5 mol% of the catalyst in toluene at room temperature for 120 h, resulting in a product yield of >99% yield

Table 2.7: Summary of the solvents screened for the BA4 and BA9–catalysed 1,3–AAI of 166b.



166b **168b**

entry[a]	catalyst (5 mol%)	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**BA9**	*p*–xylene	120	37	3
2	**BA9**	DCM	8	>99	7
3	**BA9**	DCE	8	>99	11
4[d]	**BA9**	PhMe/dioxane	120	45	7
5	**BA4**	*p*–xylene	120	52	28
6	**BA4**	DCM	120	94	20
7	**BA4**	DCE	120	77	19
8[d]	**BA4**	PhMe/dioxane	120	89	3

[a]All reactions were conducted on a 0.1 mmol scale in solvent (1 mL) with catalyst (5 mol%) at RT without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.
[d]Solvent ratio of 1:1.

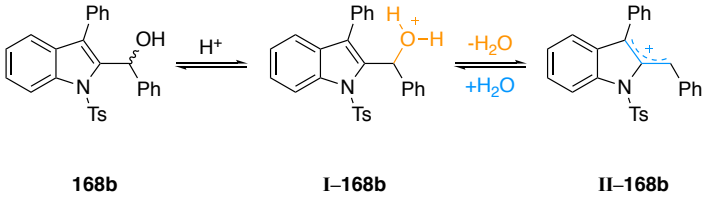
and with 4% ee (Table 2.5, entry 5). Repeating the reaction conditions with *p*–xylene instead of toluene for 120 h generated a 37% yield of **168b** and with an ee value of 3% (Table 2.7, entry 1). A survey of more polar solvents revealed the analogous reaction with DCM as the solvent for 8 h afforded the product in >99% yield along with 7% ee (entry 2). Comparable results were recorded in a control experiment using 1,2–dichloroethane as solvent (entry 3). Over 8 h, these conditions afforded a product yield of >99% and with an ee value of 11%. Employing a 1:1 mixture of toluene and dioxane as solvent produced **168b** in 45% yield along with an enantiomeric excess value of 7% (entry 4). Next, solvent effects on the enantioselective outcome of the **BA4**–catalysed 1,3–AAI of **166b** was examined. Our previous studies revealed that the most effective conditions were 5 mol% of the catalyst in toluene at room temperature for 120 h, resulting in a product yield of 56% and an ee value of 25%

(Table 2.5, entry 8). Repeating these reaction conditions with *p*–xylene instead of toluene for 120 h generated **168b** in 52% yield and with an ee value of 28% over 120 h (Table 2.7, entry 5). The more polar solvents DCM was found to afford a product yield of 94% and with 20% ee (entry 6). A similar outcome was observed in a control experiment using 1,2–dichloroethane as the solvent (entry 7). Under these latter reaction conditions, a product yield of 77% along with an ee value of 19% was obtained. The analogous reaction employing a 1:1 mixture of toluene and dioxane as solvent produced **168b** in 89% yield and with 3% ee (entry 8).

The selectivity of these types of transformations could rely on the strength and proximity of cation–counteranion interactions and, therefore, the poor solubility has the potential to greatly affect this ion pairing. However, a balance needs to be struck between the solubility of the constituents of the reaction and the solubility of the ion pair. If the ions are sufficiently soluble then the solvent will interfere with the proximity of the two, resulting in a detrimental effect on selectivity.[155]

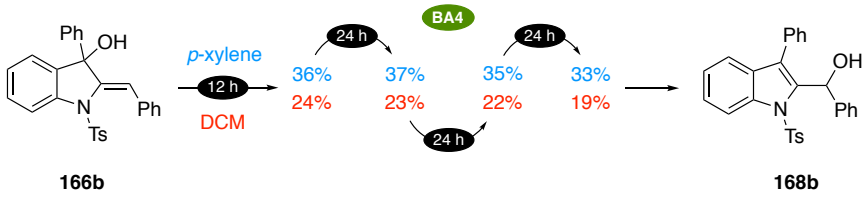
2.2.5 Evaluating the Possibility of Product Racemisation

Having achieved only moderate selectivity at this stage of our studies, we queried whether the benzylic carbon in the indolyl methanol product **168b** could be promoting racemisation under the acidic conditions (Scheme 2.9). To test this hypothesis, the product obtained under the reaction conditions described in Table 2.5, entry 8, with an ee value of 25% was remeasured by HPLC analysis after 20 days at –20 °C (Scheme 2.9). We speculated that it might be possible that protonation of the hydroxyl group and subsequent dehydration would form cationic species **II–168b**. As a result, racemisation of **168b** would be a possibility as the cationic species **II–168b** is rehydrated.



Scheme 2.9: Graphical representation of potential product racemisation.

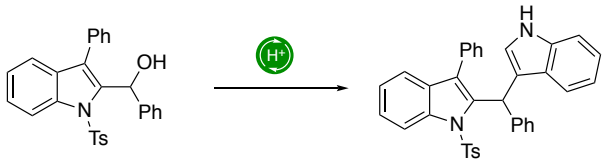
The HPLC trace acquired from the reaction described in Table 2.5, entry 8, provided an enantiomeric excess reading of 17%. This result, showing an 8% decrease in ee value, indicated that product racemisation was to be a possible factor not previously taken into consideration. In an attempt to confirm this experimental result, two further reactions were conducted. Alcohol substrate **166b** was exposed to 5 mol% of Brønsted acid catalyst **BA4** in either *p*–xylene or DCM as the solvent at room temperature over 14 h. An HPLC sample was taken at regular intervals and the enantiomeric excess value was recorded. A summary of these results is presented in Scheme 2.10. After 12 h, the reaction in *p*–xylene revealed a product enantiomeric excess value of 36%. Subsequently, the ee value was determined to be 33%, representing a decrease of 3% after 84 h. After 12 h, the reaction in DCM showed a product ee value of 24%. The ee value of the product was shown to decrease by 5% to a final value of 19% over 84 h.



Scheme 2.10: Enantiomeric excess values over time employing 5 mol% of BA4 in either *p*–xylene or DCM. Percentages represent enantiomeric excess values for 168b at each interval.

The possibility of product racemisation led us to consider whether a carbon nucleophile could be employed to trap the carbocationic intermediate of the product involved in this process. To this end, we selected indole as the nucleophilic probe for our investigations (Table 2.8). In an attempt to mitigate any solubility issues associated

Table 2.8: Indole incorporation into 168b to test for racemisation.



168b **200**

entry[a]	catalyst (5 mol%)	time (h)	additive	yield (%)	ee (%)[e]
1	**BA4**	120	4 Å MS[b]	–[c]	–
2	**BA4**	120	–	–[d]	–
3	**BA9**	120	4 Å MS[b]	–[c]	–
4	**BA9**	120	–	–[d]	–
5	**BA46**	8	–	–[d]	–

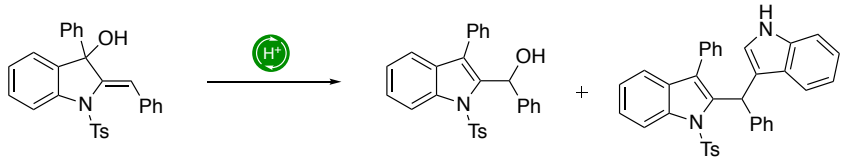
[a]All reactions were conducted on a 0.1 mmol scale with indole (1.1 eq.) in DCM (1 mL) at RT without the exclusion of air or moisture.
[b]Reaction conducted with 50 mg of 4 Å MS.
[c]No reaction based ^{1}H NMR analysis of the crude reaction mixture.
[d]Minor detection of product by mass spectrometric analysis.
[e]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

with non–polar aprotic solvents, DCM was employed for these investigations in conjunction with 5 mol% of the Brønsted acid catalyst. Our studies commenced with 0.1 mmol of a racemic sample of **168b**, 50 mg of 4 Å MS, and **BA4** as the catalyst at room temperature over 120 h (entry 1). These conditions afforded no reaction; only indolyl methanol **168b** was detected by ^{1}H NMR analysis of the crude reaction mixture. The exclusion of 4 Å MS under similar reaction conditions was found to lead to the trace detection of the indole–incorporated product **200** based on mass spectrometric analysis (entry 2). Repeating the reactions using Brønsted acid **BA9** in place of **BA4** as the catalyst afforded comparable results, where the inclusion of 4 Å MS resulted in no reaction, and their exclusion generated a trace amount of the product **200** (entries 3 and 4). Likewise, the analogous **BA46**–catalysed reaction was found to promote the incorporation of indole into the indolyl methanol **168b** after 8 h as determined by mass spectrometry (entry 5). While the results of those investigations

found only the trace detection of the diindole **200**, they hint at the possibility that indolyl methanol **168b** can dehydrate under the Brønsted acidic reaction conditions.

In an attempt to provide further support for the mechanism proposed in Scheme 2.9, the trapping of the premised cationic intermediate **II–168b** generated from **166b** by indole was next examined. The results of this investigation are summarised in Table 2.9. When exposed to 0.1 mmol of **166b** in DCM at room temperature for 120 h, 5 mol% of Brønsted acid catalyst **BA4** was found to promote only the trace incorporation of indole, as analysed by mass spectrometry (entry 1). Under similar reaction conditions, the **BA9**–mediated experiment was also shown to give only trace incorporation of indole (entry 2). In contrast, the analogous reaction catalysed by **BA46** was found to lead to no indole incorporation being detected by mass spectrometry (entry 3).[156] On the other hand, the **BA4**–catalysed reaction with *p*–xylene as the solvent was found to give the indole–incorporated product **200** in 17% yield and with 20% ee (entry 4). The indolyl methanol **168b** was additionally furnished

Table 2.9: Indole incorporation into indolinol 166b to test for racemisation.



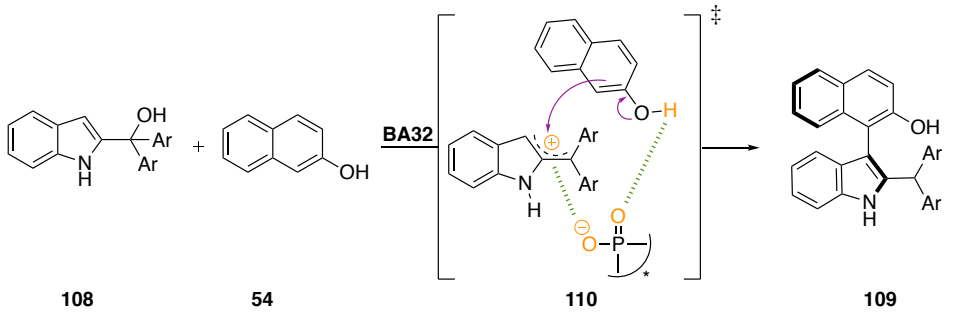
166b **168b** **200**

entry[a]	catalyst (5 mol%)	solvent	yield (%)		ee (%)	
			168b	**200**	**168b**	**200**
1	**BA4**	DCM	–[b]	–	–	–
2	**BA9**	DCM	–[b]	–	–	–
3	**BA46**	DCM	–[c]	–	–	–
4	**BA4**	*p*–xylene	34	17	42	20

[a]All reactions were conducted on a 0.1 mmol scale with indole (1.1 eq.), catalyst (5 mol%) in DCM (1 mL) at RT for 120 h without the exclusion of air or moisture.
[b]Minor detection by mass spectrometric analysis.
[c]No reaction based on ^{1}H NMR analysis of the crude reaction mixture.

in 34% yield and with 42% ee. Prior to this discovery, the most effective conditions for the 1,3–AAI of **166b** to **168b** were 5 mol% of **BA4** in *p*–xylene at room temperature for 120 h, which gave a yield of 56% along with 25% ee (Table 2.7, entry 5). This latter result hinted at the possibility that indole could be interacting with either the substrate **168b**, and/or the catalyst **BA4**, in a manner that leads to a more intimate chiral environment resulting in elevated selectivity. A similar rationale might explain the outcome of reactions with DCM as the solvent described in Table 2.9, entries 1–3. While this may also be in play, the ability of DCM to solvate such interactions might not only prevent the formation of an intimate chiral environment but also the 1,3–AAI or dehydration occurring.

During the course of this study, Li, Shi *et al.* detailed the synthesis of an axially chiral naphthyl–indole motif **109** in 56–99% yield with 82–92% ee from indolyl methanols **108** (Scheme 2.11).[74] The mechanism was proposed to involve dehydration of the substrate to form the allylic cation, and reaction *via* the transition state **110** in the presence of **BA32** as the catalyst. A feature of the work was the double–benzylic nature of the alcohol in **108** facilitating the ease of dehydration by providing a more stabilised carbocationic intermediate. We postulate that the indolyl methanol **168b** in our studies could also undergo dehydration in this manner to facilitate racemisation. In view of



Scheme 2.11: Axially chiral naphthyl–indole synthesis reported by Li, Shi *et al.* 21 examples, 56–99% yield, 82–92% ee.

the work by Li, Shi and co–works, further efforts to evaluate the potential of this line of investigation were not pursued.

2.2.6 Counteranion Partners

Various works have reported that employing catalytic salts of achiral amines, such as those shown in Figure 2.6, in conjunction with chiral BINOL–based phosphoric acid catalysts can result in the induction of high levels of enantioselectivity.[23,157] Contact ion pair species, such as **203**, do not experience solvent separation and, as a result, produce an intimate asymmetric environment. This ion pair species could potentially exist as a charged species such as **201**, or as a hydrogen bonded complex such as **202**.

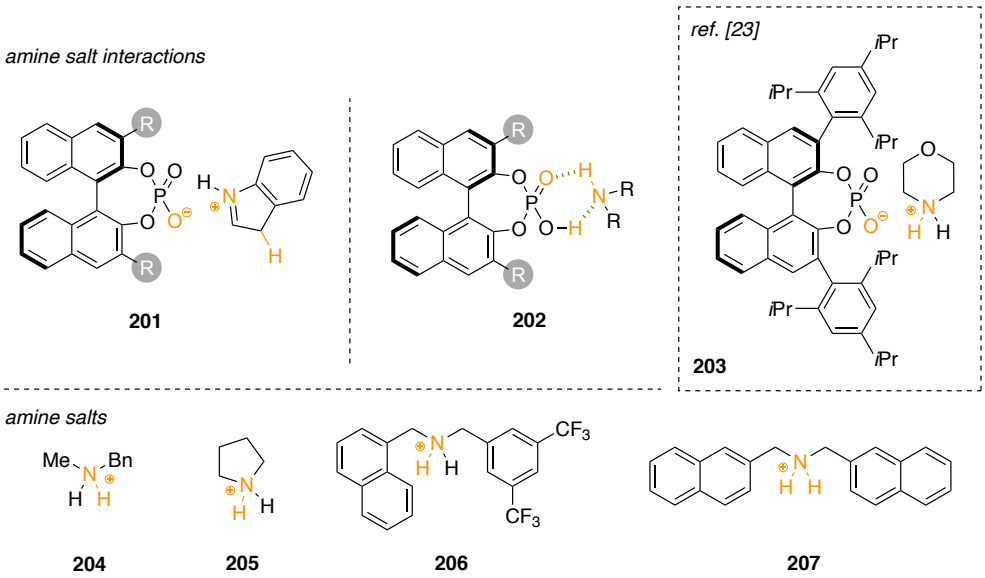
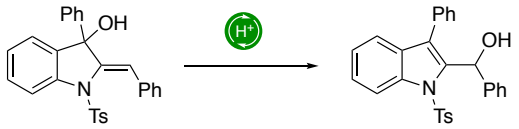


Figure 2.6: Reported achiral amine salts and phosphoric acid ion pairs.

In view of these reports and our own findings, we next moved to examine the effect of a range of achiral amines on the chiral Brønsted acid–catalysed 1,3–AAI of **166b** (Table 2.10). We hypothesised that an amine equivalent to indole that was unable to take part in nucleophilic addition could form an intimate transition state with the acid catalyst, and thereby enhance selectivity during the desired 1,3–AAI. For comparison,

the product ee values obtained in the absence on the amine additive under the conditions detailed in Table 2.10, entries 1 to 12, are included. In this study the reaction mixtures were directly measured by chiral HPLC analysis without prior purification by column chromatography. Carbazole (5 mol%) was first investigated in the reaction of **166b** subjected to 5 mol% of **BA4** in *p*–xylene at room temperature (entry 1). It was not possible, however, to determine the enantiomeric excess value of the product as it and carbazole possessed identical R_f values which prevented their separation. Repeating the reaction conditions with either morpholine or diisopropylamine was found to give a similar outcome, leading to unattainable ee values (entries 2 and 3).

Table 2.10: Investigation into achiral amines as a counteranion partners.



166b **168b**

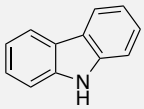
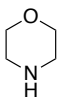
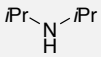
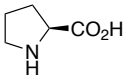
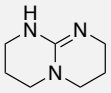
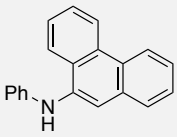
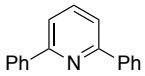
entry[a]	catalyst (5 mol%)	amine (5 mol%)	ee (%)[b]	ee (%)[b,c]
1	**BA4**		–	28
2	**BA4**		–	28
3	**BA4**		–	28
4	**BA4**		6	28
5	**BA4**		4	28
6	**BA4**		4	28

Table 2.10 continued

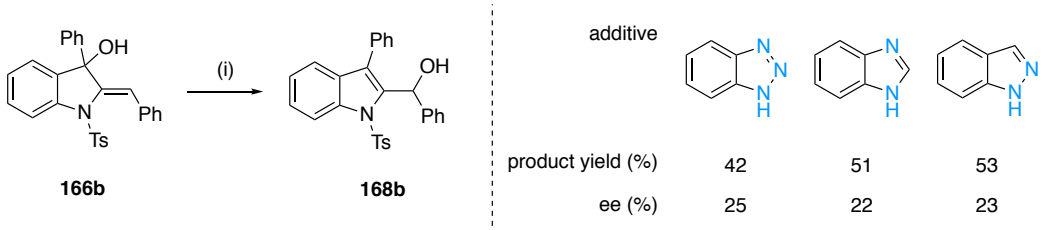
entry[a]	catalyst (5 mol%)	amine (5 mol%)	ee (%)[b]	ee (%)[b,c]
7	**BA4**		4	28
8	**BA4**		29	28
9	**BA1**		8	8
10	**BA4**		6	28
11	**BA4**		4	28
12	**BA46**		5	6

[a]All reactions were conducted on a 0.1 mmol scale with catalyst (5 mol%) in *p*–xylene (1 mL) at RT for 120 h without the exclusion of air or moisture.
[b]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.
[c]Enantiomeric excess value in the absence of the amine additive.

Reactions with dibutylamine, imidazole, *L*–proline, and triazabicyclodecene as the amine additive all failed to enhance product selectivity, affording enantiomeric excess values in the range of 4–6% (entries 4–7). In comparison, an ee value of 28% was observed in the corresponding **BA4**–mediated reaction of **166b** in the absence of the amine additive. The analogous reaction with diphenylamine as the amine additive was found to achieve an ee value of 29%, which is comparable to that found in the absence of the additive (entry 8). Repeating the reaction with **BA1** instead of **BA4** was found to give a product ee value of 8% that was comparable to that obtained in the absence of the additive (entry 9). On the basis of these finding, we speculated that diphenylamine was likely to be a spectator during the course of the transformations.

Two experiments employing a secondary amine with differing substituents were also examined (entries 10 and 11). However, these reactions employing *N*–benzylpropan–2–amine and *N*–phenylphenanthen–9–amine were found to give low product ee values of 6 and 4%, respectively. Prompted by the works of Ishihara and co–workers on the effectiveness of 2,6–diphenylpyridine and a BINSA acid in asymmetric catalysis, the reaction of **166b** in the presence of the aromatic heterocycle and **BA46** in *p*–xylene at room temperature was attempted (entry 12).[158] Under these reaction conditions, the indolyl methanol **168b**, however, was afforded in a low ee value of 5%.

With the strategy of employing various achiral amine salts shown to be unsuccessful, we next moved to introduce additives more akin to the indole structure such as benzotriazole, benzimidazole, and indazole (Scheme 2.12). In an initial experiment this revealed exposing 0.1 mmol of **166b** to 5 mol% of **BA4** in *p*–xylene to 1 equivalent of benzotriazole at room temperature over 120 h afforded **168b** in a 42% yield with an ee value of 25%. Repeating the reaction conditions with benzimidazole in place of benzotriazole generated indolyl methanol **168b** in 51% yield and with 22% ee. Similarly, in the presence of 5 mol% of indazole as the additive, the analogous **BA4**–mediated reaction was found to give a product yield and ee value of 53 and 23%, respectively.

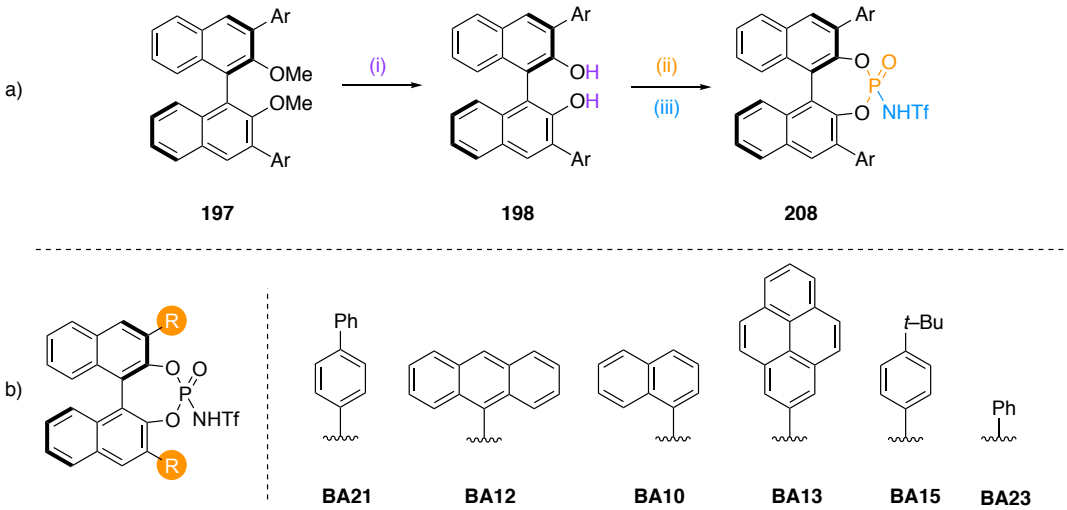


Scheme 2.12: Nitrogen heterocycles employed to induce enantioselectivity. i) BA4 (5 mol%), additive (1 eq.), *p*–xylene, 120 h.

2.2.7 Exploring the Use of Chiral Phosphoramide Catalysts

With the low to moderate product ee values obtained from the reactions of **166b** mediated by the phosphoric acid catalysts, attention was turned to exploring the more acidic BINOL–based phosphoramides (Scheme 2.13).

The phosphoramide catalyst **208** was first introduced by Yamamoto *et al.* in studies directed toward realising the asymmetric Diels–Alder reaction of α,β–unsaturated ketones with siloxydienes to give the resulting Diels–Alder adduct in yields and ee values of >99 and ≤93%, respectively.[159] Its synthesis involved the initial boron–mediated deprotection of **197** to afford the diol **198**. Phosphorylation of **198** under basic conditions, followed by the addition of $TfNH_2$ in anhydrous propionitrile afforded phosphoramide **208**. Following flash column chromatography, phosphoramide **208** is washed with 6 M HCl to remove any potential metal impurities and isolated in 32% yield over three steps.[153] The phosphoramides **BA21**, **BA12**, **BA10**, **BA13**, **BA15**, and **BA23** were synthesised following this procedure. The

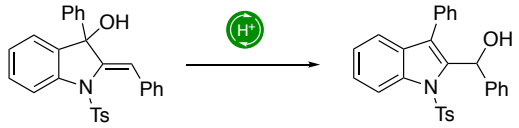


Scheme 2.13: a) BINOL–based phosphoramide catalyst synthesis. i) BBr_3 (7 eq.), DCM. ii) Anhydrous DCM, distilled Et_3N, $POCl_3$, DMAP. iii) $TfNH_2$, anhydrous EtCN. Ar = phenyl, 32% product yield over three steps. b) Procured chiral phosphoramide acid catalysts.

difficulty associated with this set of syntheses was significant; the sensitivity of the proposed PO_3Cl intermediate to hydrolysis is considerable and poses a serious obstacle to obtaining these catalysts as the only adduct. If the distilled triethylamine or propionitrile were not sufficiently dry, the phosphoric acid was obtained.

With the phosphoramide catalysts in hand, we commenced our investigation by examining their ability to asymmetrically catalyse the 1,3–AAI of **166b** (Table 2.11). In the first instance, the *t*–butylphenyl–substituted phosphoramide catalyst **BA15** was examined (entry 1). Treatment of 0.1 mmol of indolinol **166b** with 5 mol% of this Brønsted acid in *p*–xylene at room temperature over a 120 h period afforded a 76% product yield along with an ee value of 11% (entry 1). Repeating the reaction conditions with the biphenyl–substituted catalyst **BA21** for 20 h afforded a product yield and ee value of >99% and 13%, respectively (entry 2). Similarly, the

Table 2.11: Summary of the chiral phosphoramide screen for the Brønsted acid–catalysed 1,3–AAI of 166b



166b **168b**

entry[a]	catalyst (5 mol%)	time (h)	yield (%)[b]	ee (%)[c]
1	**BA15**	120	76	11
2	**BA21**	20	>99	13
3	**BA12**	1	>99	3
4	**BA23**	0.25	>99	2
5	**BA10**	0.25	>99	10
6	**BA13**	0.25	>99	14
7[d]	**BA13**	3	>99	13

[a]All reactions were conducted on a 0.1 mmol scale with catalyst (5 mol%) in *p*–xylene (1 mL) at RT without the exclusion of air or moisture.
[b]^{1}H NMR yield CH_2Br_2 used as internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.
[d]Reaction conducted at –40 °C in toluene.

anthracenyl–substituted phosphoramide **BA12**–mediated reaction after 1 h produced **168b** in >99% yield and 3% ee (entry 3). Changing the catalyst to the phenyl–substituted **BA23** after 0.25 h gave a product yield of >99% along with 2% ee (entry 4). The naphthyl–substituted Brønsted acid **BA10**–catalysed reaction provided generated **168b** in >99% yield and with an ee value of 10% (entry 5). With the pyrenyl–substituted phosphoramide **BA13** as the catalyst, a product yield and enantiomeric excess value of >99 and 14%, respectively, was obtained (entry 6). As the **BA13**–catalysed 1,3–AAI of **166b** were found to be the most effective out of this set of experiments, the reaction conditions were performed once more in toluene at –40 °C (entry 7). The experiment was carried out to determine if a greater degree of enantioselectivity could be achieved at a lower reaction temperature. The switch to toluene at this point was necessary as the melting point of *p*–xylene is *ca*. 13 °C. However, under these latter reaction conditions, a similar outcome was observed, with the product being afforded in near quantitative yield and with an ee value of 13%.

In view of the low product ee values obtained from the BINOL–based Brønsted acids, attention was turned to the VANOL– and menthol–based Brønsted acids **BA49** and **BA50** (Figure 2.7). **BA49** was prepared in 31% yield over these steps from its diol **209** involving phosphorylation with $POCl_3$, addition of $TfNH_2$, and acidification (Figure 2.7a). Cyclopentadieneyl catalyst **BA50** was synthesised in three steps following reported procedures (Figure 2.7b).[160,161] This involved the addition of dimethylmalonate to dimethylacetylene dicarboxylate in acidified pyridine and subsequent treatment with potassium acetate to afford the cyclic adduct **212** in 45% yield over two steps. Subsequent treatment with an excess of (–)–menthol in the presence of *N*–methylimidazole in toluene at reflux furnished the desired chiral derivative in 90% yield. This cyclopentadienyl catalyst was an attractive target due to

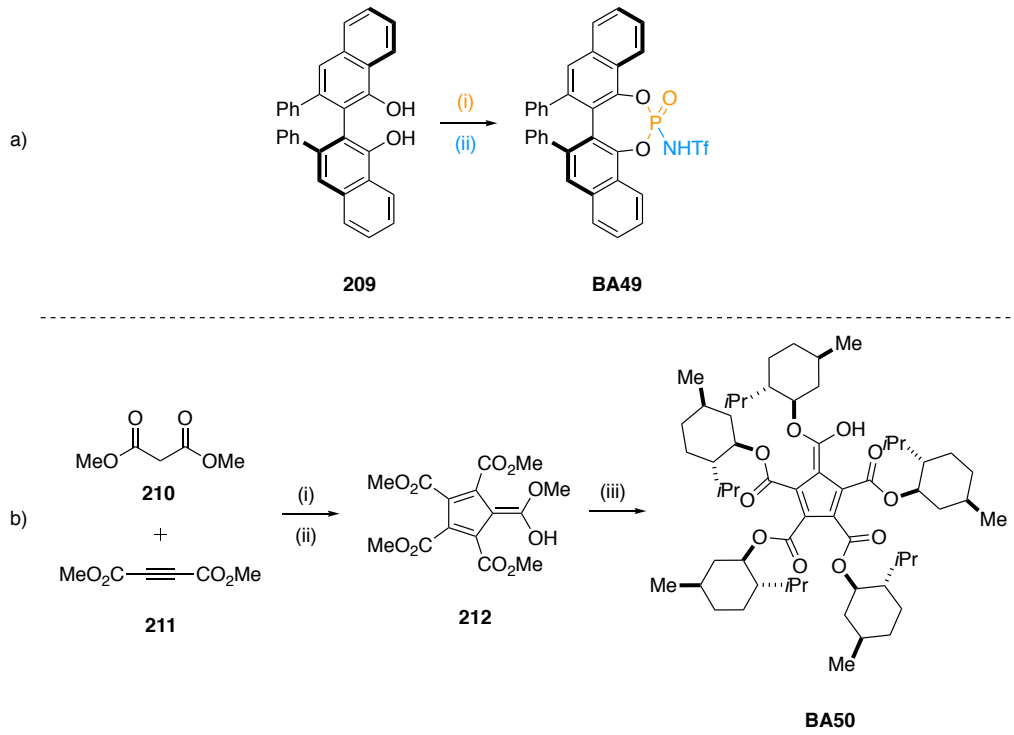


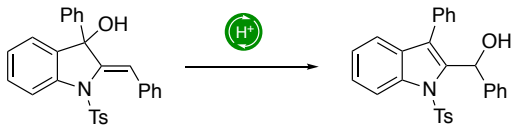
Figure 2.7: a) Synthesis of VANOL–based phosphoramide catalyst BA49. i) Anhydrous DCM, distilled Et_3N, $POCl_3$, DMAP. ii) $TfNH_2$, anhydrous EtCN, 31% yield. b) Synthesis of menthol–based acid catalyst BA50. i) Pyridine, AcOH. ii) KOAc; HCl, 45% yield over two steps. iii) (–)–Menthol, NMI, PhMe, reflux, 48 h, 90% yield.

its reported ability to outperform chiral phosphoric acids in organocatalysis, with catalyst loadings as low as 0.01 mol%.[33,161] It was envisioned that a Brønsted acid containing a different sterically and space–occupying backbone to that of BINOL might provide the opportunity to realise a more intimate chiral environment for asymmetric induction.

We moved to investigate the effect of these catalysts on the 1,3–AAI of **166b** to indolyl methanol **168b** (Table 2.12). This revealed that subjecting 0.1 mmol of indolinol substrate **166b** to 5 mol% of **BA49** in *p*–xylene at room temperature for 120 h furnished **168b** in 47% yield and 2% ee (entry 1). Repeating the reaction conditions with **BA49** in DCM was able to reduce the reaction time to 20 h to deliver a product yield of >99% and with a 13% ee value (entry 2). The analogous reaction with the menthol–based catalyst **BA50** in *p*–xylene at room temperature for 120 h was found

to lead to a product yield of 64% along with an ee value of 4% (entry 3). Similarly, changing to solvent to DCM was observed to give a similar outcome, with **168b** furnished in 60% yield and with 3% ee (entry 4).

Table 2.12: Summary of the VANOL– and (–)–menthol–based Brønsted acid–catalysed 1,3–AAI of 166b.



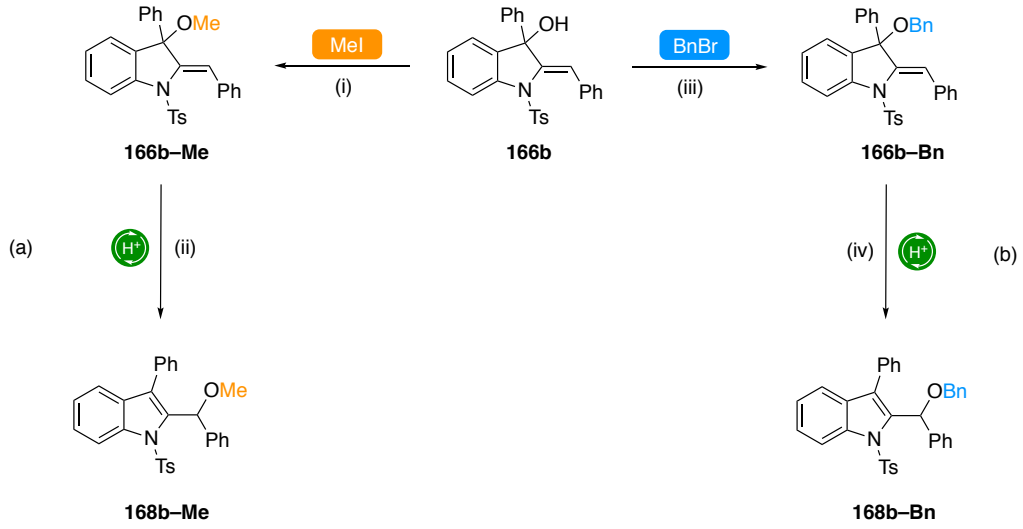
166b **168b**

entry[a]	catalyst (5 mol%)	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	**BA49**	*p*–xylene	120	47	2
2	**BA49**	DCM	20	>99	13
3	**BA50**	*p*–xylene	120	64	4
4	**BA50**	DCM	120	60	3

[a]All reactions were conducted on a 0.1 mmol scale in solvent (1 mL) with catalyst (5 mol%) at RT without the exclusion of air or moisture.
[b]^{1}H NMR yield CH_2Br_2 used as internal standard.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak OD column, 10% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

2.2.8 Evaluating the Migrating Group

With an asymmetric 1,3–AAI of **166b** remaining elusive, we speculated whether a larger alkoxy migrating group in place of the hydroxyl motif might lead to an increase in product enantioselectivity. We postulated that a larger and more sterically demanding alkoxy motif might migrate more slowly and, in the process, participate in stronger hydrogen–bonding interactions with the catalyst. The alkoxyindole product might also be anticipated to be less prone to undergo racemisation under the acidic reaction conditions. With this in mind, the 3–indolyl methyl ether **166b–Me** was prepared in 72% yield by treating the alcohol substrate **166b** to MeI under basic conditions in THF (Scheme 2.14). Likewise, the indole benzyl ether **166b–Bn** was synthesised in 81% yield by exposing indole alcohol **166b** to BnBr under basic conditions in THF. Treating the 3–indolyl methyl ether **166b–Me** to 5 mol% of the



Scheme 2.14: Investigations into the effect of a larger migrating group on enantioselectivity. a) (i) MeI (1.1 eq.), NaH (1.1 eq.), THF, 72% yield. (ii) BA4 (5 mol%), *p*–xylene, RT, 120 h, 12% yield, 12% ee, 88% yield rcsm. b) (iii) BnBr (1.1 eq.), NaH (1.1 eq.), THF, 81% yield. (iv) BA4 (5 mol%), *p*–xylene, RT, 120 h, 65% yield, 0% ee.

Bronsted acid **BA4** in *p*–xylene at room temperature for 120 h revealed the isomerisation product **168b–Me** was furnished in 12% yield along with an enantiomeric excess of 12%. The starting material **166b–Me** was recovered in 88% yield after column chromatography. Under similar reaction conditions, the **BA4**–catalysed isomerisation of the 3–indolyl benzyl ether **166b–Bn** was found to give the corresponding 2–benzyloxy–1*H*–indole adduct **168b–Bn** as a racemate in 65% yield.

2.3 Conclusion

In summary, a wide variety of chiral Brønsted acid catalysts, shown in Figure 2.8, and reaction conditions were investigated to identify the optimum conditions to mediate the first asymmetric 1,3–AAI of 3–indolinols to 2–indolyl methanols. Although excellent yields and short reaction times were achieved, the asymmetric 1,3–allylic alcohol isomerisation to provide indolyl methanols in a highly enantioselective manner remained unrealised. Our studies showed the best result obtained was accomplished on subjecting indolinol **166b** to 5 mol% of catalyst **BA4** in DCM for 120 h. These

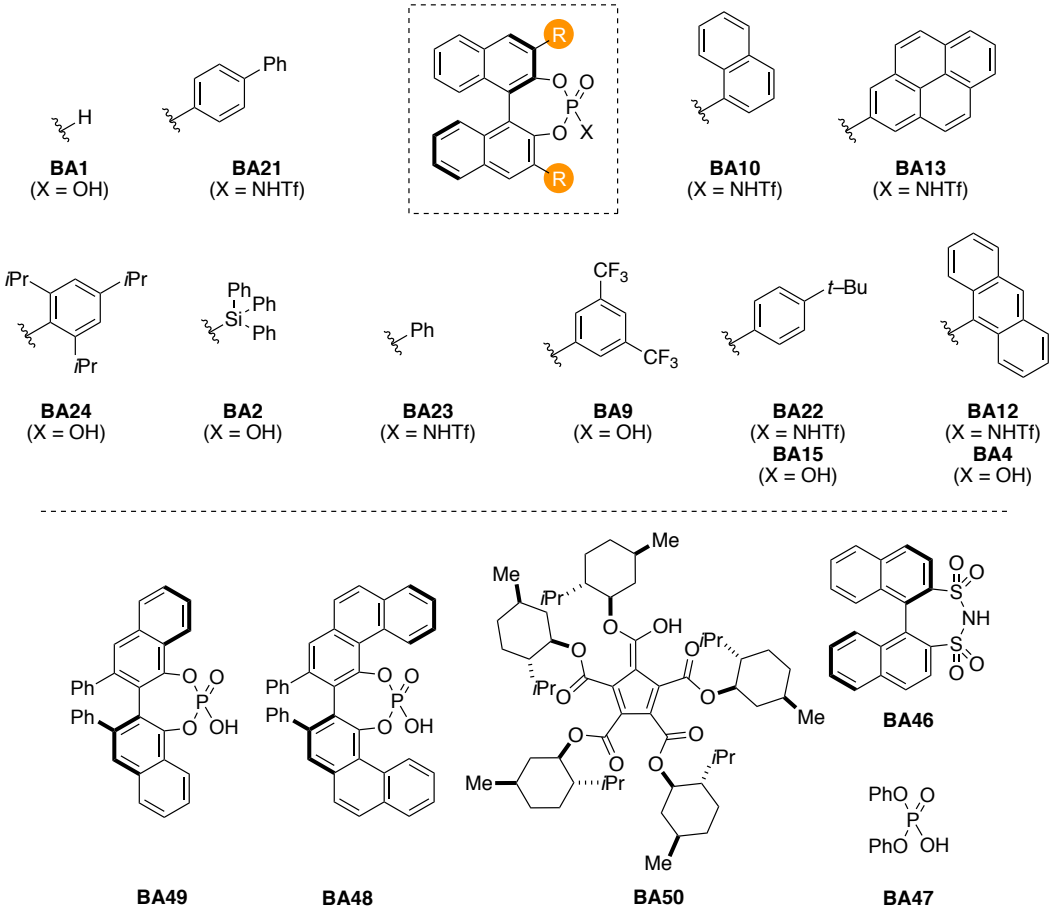
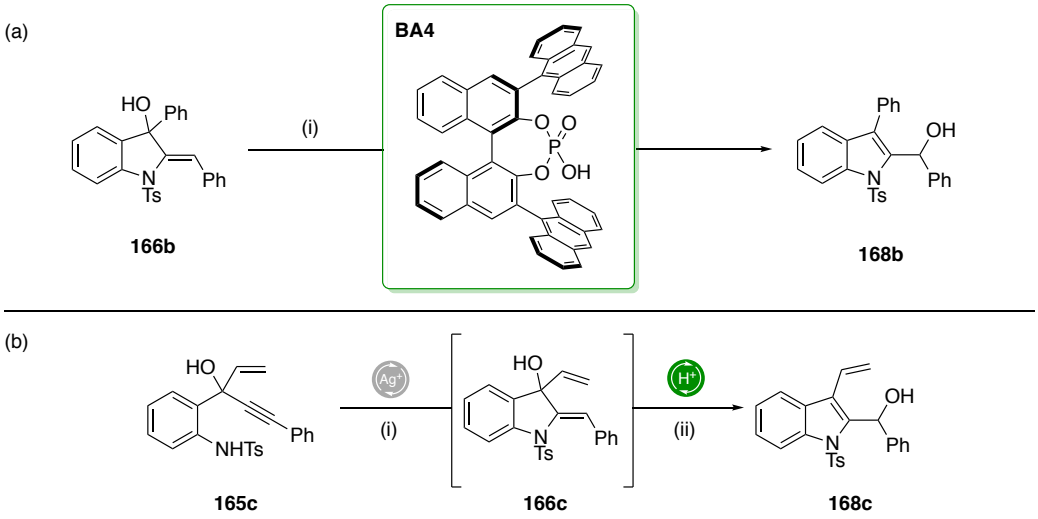


Figure 2.8: Chiral Brønsted acid catalysts employed during this cycloisomerisation/1,3–AAI study.

conditions afforded the 1,3-AAI product **168b** in 92% yield with an ee value of 20% (Scheme 2.15a). During the course of this work, Ramasastry and co–workers also reported a one–pot procedure involving AgOAc–catalysed 5–*exo*–*dig* cyclisation of **165c** to **166c** and subsequent Brønsted acid–mediated 1,3–AAI to indolyl methanol **168c** (Scheme 2.15b).[162] The conditions employed in this latter study involved the use of 10 mol% of the VAPOL–based Brønsted acid **BA48** in 1,2–dichloroethane for 48 h which gave **168c** in 22% yield with an ee value of 92%. Thus, our findings, and that of the Ramasastry group, have shown that the asymmetric 1,3–AAI reaction remains a formidable challenge in organic synthesis.



Scheme 2.15: a) Optimised conditions for the 1,3-AAI of **166b** to **168b**. (i) **BA4** (5 mol%), DCM, RT, 120 h. b) Works reported by Ramasastry *et al.* towards an asymmetric 1,3–AAI. (i) AgOAc (2 mol%), DCE, 60 °C, 3 h, then (ii) **BA48** (10 mol%), 0 °C, 48 h, 22% yield, 92% ee.

Chapter 3

3.0 Brønsted Acid–Catalysed Allylic Amination of 1–(2–Aminoaryl)prop–2–en–1–ols to 1,2–Dihydroquinolines

3.1 Introduction

The quinoline heterocycle features prominently in a myriad bioactive natural products and functional materials (Figure 3.1).[163–165] For example, natural products containing the quinoline motif include the alkaloid virantmycin **213**, an antiviral agent active against various viral strains,[166,167] martinellic acid **214**,[168] found in the root of the tropical plant *Martinella iquitosensis*, and angustureine **215**,[169] isolated from the

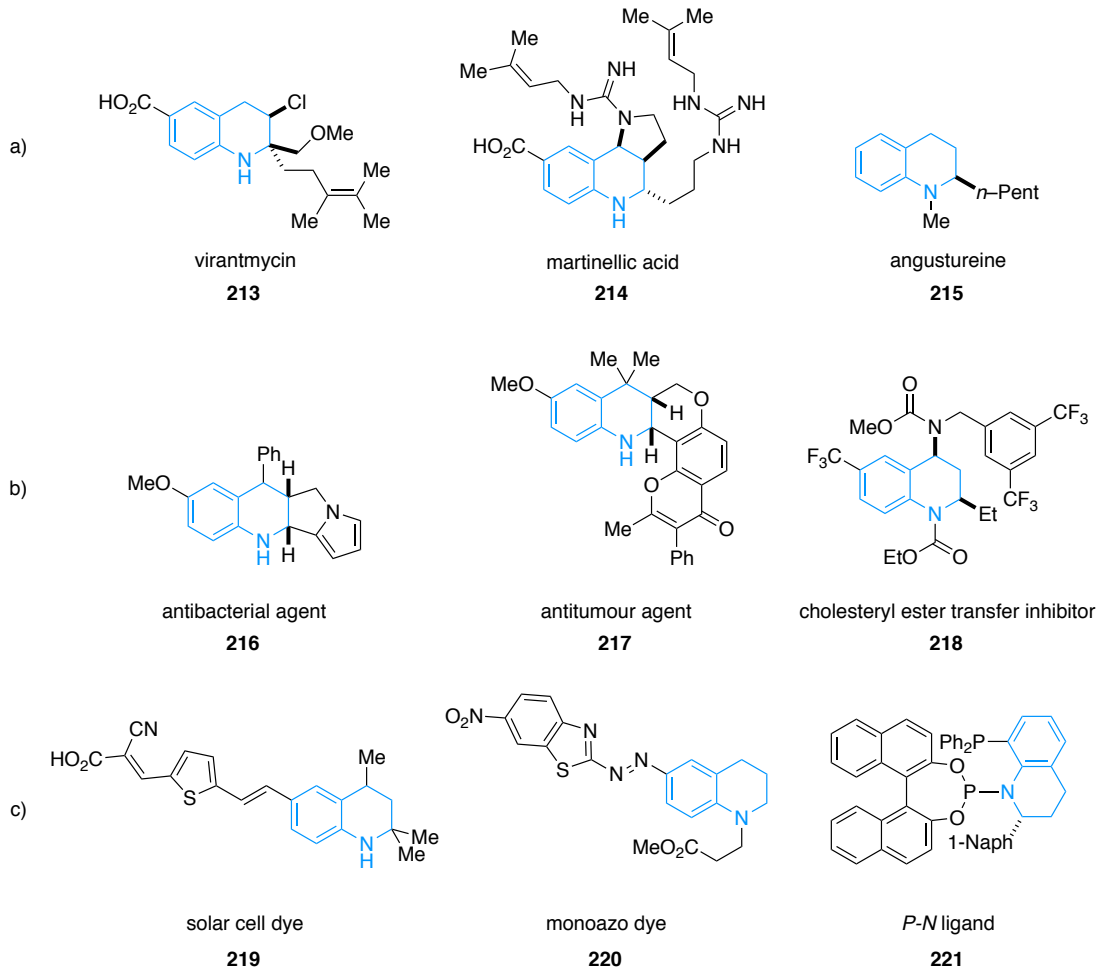
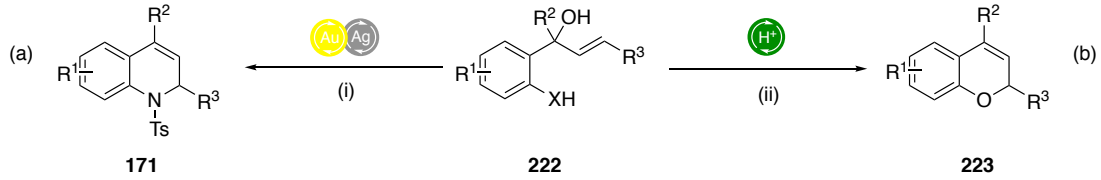


Figure 3.1: a) Selected quinoline derivatives featured in natural products. b) Selected pharmacologically relevant quinolines. c) Selected functional materials featuring the quinoline core structure.

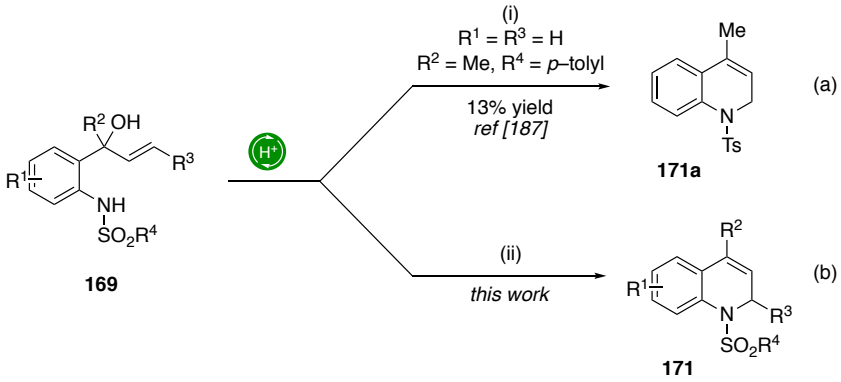
South American *Galipea officinalis* tree bark (Figure 3.1a). The activity of pharmacologically relevant quinolines include the antibacterial agent **216**, shown to be effect against various strains including *E. coli* and *S. aureus* (Figure 3.1b). Antitumour agent **217** has displayed activity against breast cancer cell lines, and the hormone inhibitor **218** functions as a cholesteryl ester transfer protein inhibitor.[170–175] Quinolines have also been found to be an important component in dye–sensitized solar cells such as **219**, and the monoazo dye **220** (Figure 3.1c). In addition to this is their application as a ligand such as the chiral phosphine–phosphoramidate used for asymmetric metal–catalysed hydrogenations of olefins.[176–179] The *N*–heterocyclic motif, both fully and partially hydrogenated, is also a versatile building block in various strategies to synthetically valuable products.[180–187] As a result, the discovery of efficient synthetic methods using mild conditions to produce this member of the *N*–heterocyclic family continues to be actively pursued.[45,180a]

Recent reports have demonstrated both Brønsted and Lewis acid–catalysed reactions of allylic and homoallylic alcohols to be powerful synthetic tools to rapidly increase molecular complexity.[45,188a] For instance, we recently described a method for the synthesis of 1,2–dihydroquinolines in 42–91% yield that relied on Au(III)–catalysed allylic amination of 1–(2–aminoaryl)prop–2–en–1–ols (Scheme 3.1a).[187] Following this work, Rueping *et al*. reported an asymmetric approach to 2*H*–chromenes in 61–95% yield and 86–96% ee from the chiral Brønsted acid–catalysed intramolecular allylic substitution of 2–(1–hydroxy–3–arylallyl)phenols (Scheme 3.1b).[196] The prospect of scale–up strategies for the Au(III)–mediated protocol for 1,2–dihydroquinolines synthesis were deemed low, however, due to the need for high catalyst loadings and cost of the metal salts. In this context, it was proposed that



Scheme 3.1: a) Au(III)–catalysed allylic amination. i) $AuCl_3$ (5 mol%), $AgSbF_6$ (15 mol%), PhMe, RT, 1 h. 18 examples, 42–91% yield. b) Brønsted acid–catalysed allylic substitution. ii) H_8–BA23 (5–10 mol%), PhMe, –78 °C, 24 h. 14 examples 61–95% yield, 84–96% ee.

the development of the Brønsted acid–mediated version of this *N*–heterocyclic–forming transformation could form the basis for readdressing these limitations. Low–cost, commercially available, and highly tolerant to air and moisture, Brønsted acids have been demonstrated to be versatile for catalysing a broad range of functional group transformations.[197] We were also encouraged by the outcome of an experiment in an earlier study that revealed the *p*–TsOH–mediated reaction of the 1,2–amino alcohol **169** provided the expected *N*–heterocycle **171a** in 13 % yield (Scheme 3.2a). Added to this was a recent report detailing a thiourea–HBr co–catalytic procedure, although restricted to aryl–substituted starting materials, that allowed access to the *N*–heterocycle.[45,183] In this chapter, we describe the Brønsted acid–mediated allylic amination of a variety of 1–(2–aminoaryl)prop–2–en–1–ols (Scheme 3.2b). Achieved at a low catalyst loading of 0.01 mol%, a series of 1,2–dihydroquinolines were



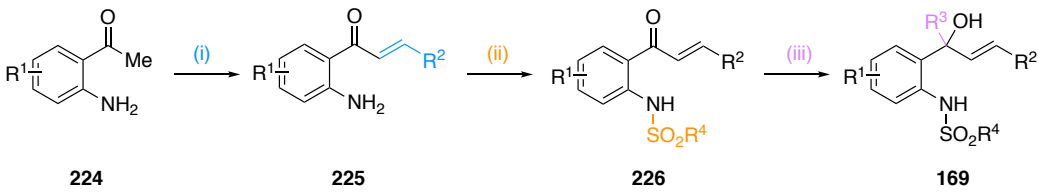
Scheme 3.2: Brønsted–mediated allylic amination of 1–(2–aminoaryl)prop–2–en–1–ols **169**. (i) *p*–TsOH (5 mol%), PhMe, RT, 16 h. (ii) TfOH (0.01 mol%), PhMe, RT.

obtained in good to excellent yields without the need for the exclusion of air or moisture.

3.2 Results and Discussion

3.2.1 The Synthesis of the Starting Materials

All 1–(2–aminoaryl)prop–2–en–1–ols presented in this study were prepared from the appropriate *o*–anilinyl methyl ketones in three steps using known methods (Scheme 3.3).[198] This involved an initial base–catalysed aldol condensation of ketone **224** with the appropriate aldehyde to give the enone **225**. This is followed by sulfonylation with 4-toluenesulfonyl chloride and pyridine to afford a range of *N*–sulfonyl chalcones **226**. Subsequent $NaBH_4$–mediated reduction of the aryl ketone allowed access to the secondary allylic alcohol substrate **169** (R^3 = H) in 53–90% yield over three steps. Alternatively, reaction of **226** with the appropriate Grignard reagent provided the tertiary allylic alcohol substrates **169** (R^3 = aryl, alkyl) in 51–90% yield over three steps.



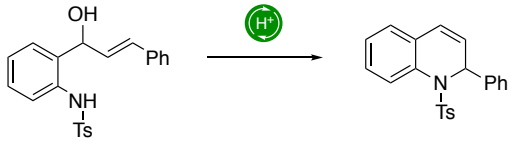
224 **225** **226** **169**

Scheme 3.3: Synthesis of 1–(2–aminoaryl)prop–2–en–1–ols **169** from *o*–anilinyl methyl ketones **224**. i) R^2CHO, NaOH, EtOH, 56–87% yield. ii) R^4SO_2Cl, Pyridine, 86–98% yield. iii) R^3 = H: $NaBH_4$ (5 eq.), MeOH, 53–90% yield, or R^3 = aryl/alkyl: R^3MgBr (5 eq.), THF, 51–76% yield.

3.2.2 Optimisation of the Reaction Conditions

With allylic alcohol **169b** as the model substrate, we commenced our study to identify the optimum Brønsted acid-catalysed dehydrative cyclisation conditions (Table 3.1). Initial experiments of this study revealed that 10 mol% of *p*–TsOH in toluene at room

Table 3.1: Optimisation of the reaction conditions for the Brønsted acid–mediated cyclisation of allylic alcohol **169b** to 2*H*–quinoline **171b**.



169b **171b**

entry[a]	catalyst	loading (%)	solvent	time (h)	yield (%)[b]
1	*p*–TsOH	10	PhMe	72	32
2	12 M HCl	10	PhMe	16	33
3	$(PhO)_2PO_2H$	10	PhMe	16	20
4	TfOH	10	PhMe	0.25	79
5	TfOH	10	DCM	3	47[c]
6	TfOH	10	THF	4	52[c]
7	TfOH	10	EtOAc	3	38[c]
8	TfOH	10	MeCN	2	41[c]
9	TfOH	10	EtOH	3	46[c]
10	TfOH	1	PhMe	1	65
11	TfOH	0.1	PhMe	2	76
12	TfOH	0.01	PhMe	3	78
13	TfOH	0.01	DCM	6	45

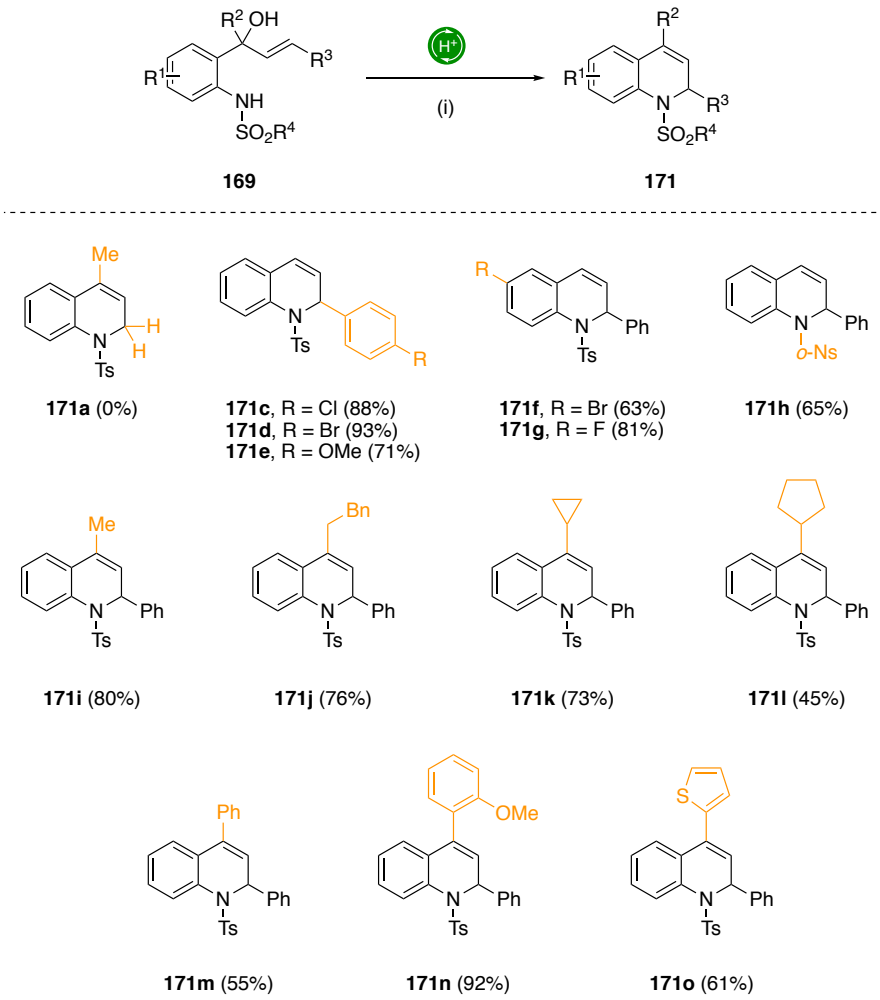
[a]All reactions were conducted on a 0.2 mmol scale in solvent (2 mL) without the exclusion of air or moisture.
[b]Isolated yield.
[c]^{1}H NMR yield determined using CH_2Br_2 as the internal standard.

temperature for 72 h produced **171b** in 32% yield (entry 1). Conducting the reaction with 12 M HCl or diphenylphosphinic acid as the catalyst in place of *p*–TsOH afforded product yields of 33% and 20%, respectively (entries 2 and 3). To explore the effects of a more acidic catalyst, when TfOH in place of *p*-TsOH was employed, the desired quinoline was afforded in 79% yield after 0.25 h (entry 4). Subsequent experimentation focussing on the effect of solvent on the desired transformation with TfOH as the catalyst revealed employing dichloromethane gave the desired *N*–heterocycle in 47% yield after 3 h (entry 5). Similar results were obtained in reactions

with either THF or EtOAc as the solvent, affording product yields of 52 and 38% after 4 and 3 h, respectively (entries 6 and 7). No improvement in product yield was found on repeating the reaction in more polar solvents such as MeCN and EtOH (entries 8 and 9). In these experiments, product yields of 41 and 46% were obtained after 2 and 3 h. With toluene found to be the best solvent, the reaction at different catalyst loadings was next explored (entries 10–13). This found that decreasing the catalyst loading from 10 to 1 to 0.1 to 0.01 mol% showed no significant loss in conversion, with **171b** obtained in 65–78% yield (entries 10–12). In each experiment, however, a ten–fold decrease in catalyst loading did require an additional hour of reaction time. However, the analogous reaction at a catalyst loading of 0.01 mol% with DCM in place of toluene was shown to give a lower product yield of 45% after 6 h (entry 13). Based on the above results, the optimum reaction conditions for the transformation of **169b** to **171b** was found to be 0.01 mol% of TfOH in toluene at room temperature for 3 h (entry 12).

3.2.3 Determining the Scope of the Catalytic Method

To assess the generality of the present optimised procedure, our attention next turned to the reactions of a number of 1–(2–aminoaryl)prop–2–en–1–ols **169a** and **169c–o** (Scheme 3.4). In general, these studies demonstrated that the TfOH–mediated experimental conditions were wide in scope and an array of substituted 1,2–dihydroquinolines **171c**–**o** could be afforded in good to excellent yields. Reactions of substrates with an electron–withdrawing or –donating group featured at the *para*–position of the styryl group **169c–e** were found to be well tolerated and furnished the corresponding products **171c–e** in good to excellent yields of 64–93%. Similarly, substrates with an electron–withdrawing group at the *para*–position of the anilinyl group **169f** and **169g** were shown to cyclise efficiently to the corresponding 1,2–



Scheme 3.4: TfOH–catalysed allylic amination of 1–(2–aminoaryl)prop–2–en–1–ols **169**. i) All reactions were conducted on a 0.2 mmol scale with TfOH (0.01 mol%) in toluene (3 mL) at room temperature for 2–10 h. Values in parentheses denote isolated product yields.

dihydroquinolines **171f** and **171g** in yields of 63 and 81%, respectively. The reaction of a starting alcohol featuring an *ortho*–nosyl–protected group (**169h**) cyclised smoothly, giving **171h** in a product yield of 65%. Substrates with a pendant alkyl (**169i,j**) or cycloalkyl (**169k,l**) group at the tertiary carbinol carbon centre were also found to provide the corresponding 1,2–dihydroquinolines **171i–l** in 45–80% yield, with the structure of **171j** determined by X–ray crystallographic analysis (Figure 3.2). The reactions of tertiary alcohol substrates featuring an aryl (**169m** and **169n**) or thiophenyl (**169o**) moiety were revealed to proceed well. These experiments delivered the corresponding 1,2–dihydroquinolines **171m–o** in 55–92% yield. The structures of

171m and **171n** were also confirmed by X–ray crystallographic analysis (Figure 3.3). However, the present protocol was discovered to be restricted to substrates comprising an aryl–substituted alkene motif. The TfOH–mediated experiment of **169a**, containing a terminal alkene moiety, was found to produce a mixture of decomposition products that could not be identified by ^{1}H NMR analysis.

On the other hand, the present Brønsted acid–meditated allylic aminations revealed that the nitrogen ring–forming reaction was highly selective, with the 1,2–dihydroquinolines being obtained as a single product. The potential for the formation of side–products as a consequence of competitive hydroamination, Friedel–Crafts or dehydration reactions were not observed by ^{1}H NMR measurements of the crude reaction mixtures. With these results in hand, we next examined whether the analogous asymmetric reaction of the newly designed Brønsted acid–catalysed process could be realised.

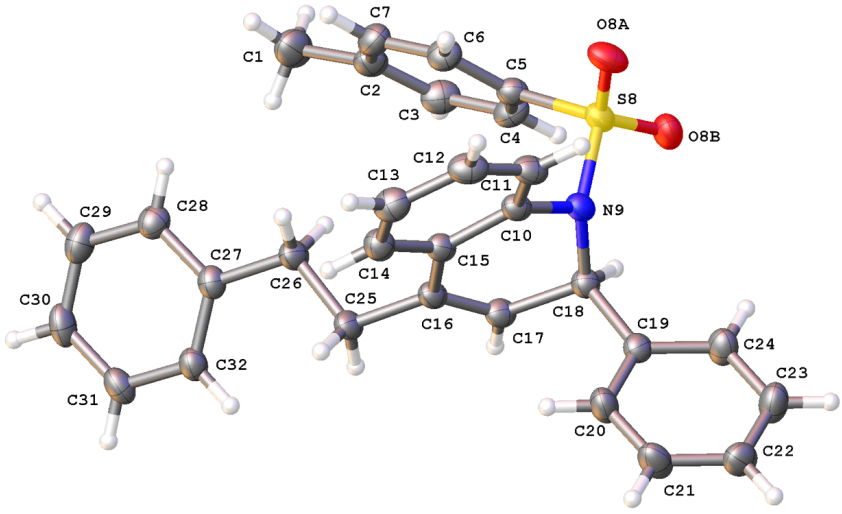
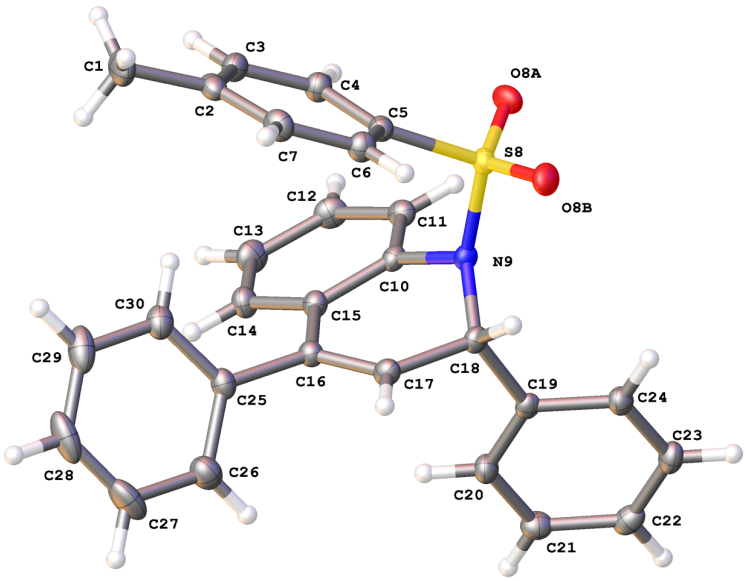


Figure 3.2: ORTEP drawing of 4–phenethyl–2–phenyl–1–tosyl–1,2–dihydroquinoline **171j** with thermal ellipsoids at 50% probability levels.[271]

(a)



(b)

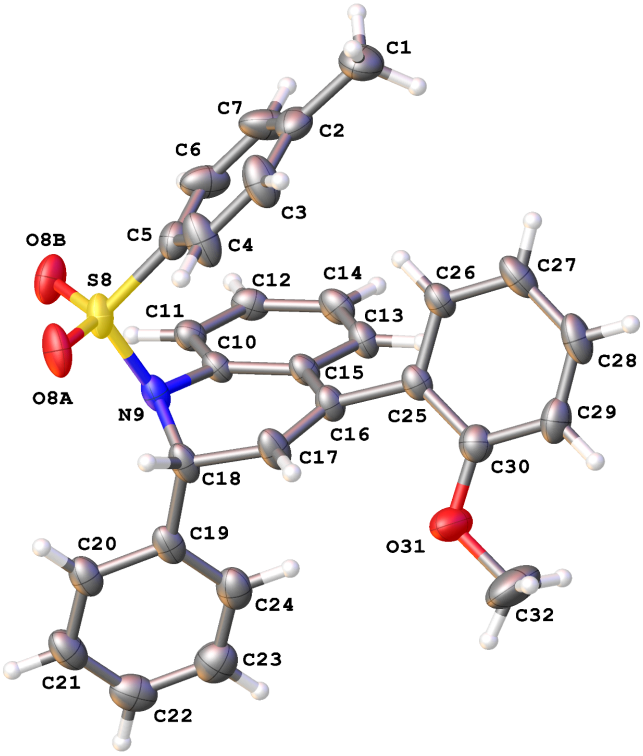


Figure 3.3: a) ORTEP drawings of 4–(2–methoxyphenyl)–2–phenyl–1–tosyl–1,2–dihydroquinoline **171n** and 2,4–diphenyl–1–tosyl–1,2–dihydroquinoline **171m** with thermal ellipsoids at 50% probability levels.[271]

3.2.4 Development of the Chiral Brønsted Acid–Catalysed Asymmetric Allylic Amination of 1–(2–Amino)prop–2–en–1–ols

To evaluate whether an asymmetric version of the present 1,2–dihydroquinoline formation reaction could be realised, the cyclisation of allylic alcohol **169b** mediated by a variety of chiral Brønsted acids were investigated (Table 3.2). Our study commenced with the treatment of the substrate **169b** with 5 mol% of the biphenyl–substituted phosphoramide catalyst **BA1** in toluene at room temperature for 0.3 h (entry 1). The reaction proceeded smoothly, giving a product yield of 74% and an enantiomeric excess value of 27%. Decreasing the reaction temperature to 0 °C for 2 h was found to improve the product yield and ee value to 89 and 35%, respectively (entry 2). The introduction of 4 Å MS to these latter reaction conditions gave a lower

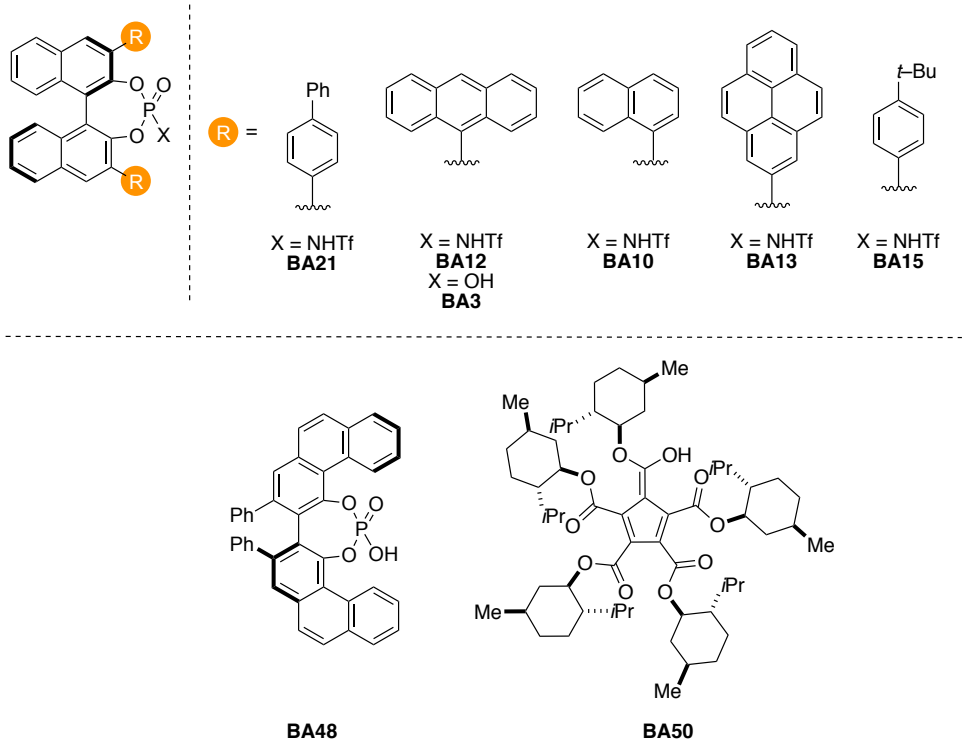
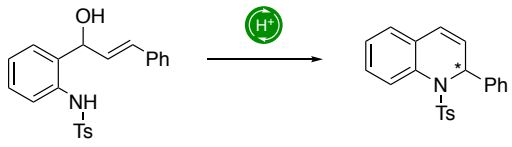


Figure 3.4: Chiral Brønsted acids employed during the optimisation of the asymmetric synthesis of 1,2–dihydroquinoline **171b**.

product yield of 50% and an ee value of 37% (entry 3). Unfortunately, the anthracenyl–substituted phosphoramide catalyst **BA12** was unable to catalyse the desired cyclisation and no reaction was observed (entry 4). In contrast, the anthracenyl–substituted phosphoric acid variant **BA4** was found to catalyse the reaction at room temperature for 30 h, affording the desired product **171b** in 70% yield and with 17% ee (entry 5). The 1–naphthyl–substituted phosphoramide catalyst **BA10** was next examined at 0 °C for 2 h and was shown to catalyse the desired transformation to give a product yield of 49% along with 2% ee (entry 6). Under similar reaction conditions,

Table 3.2: Optimisation of the asymmetric allylic amination of 1–(2–aminoaryl)prop–2–en–1–ol **171b**.



169b **171b**

entry[a]	catalyst	time (h)	temp. (°C)	yield (%)[b]	ee (%)[c]
1	**BA21**	0.3	RT	74	27
2	**BA21**	2	0	89	35
3[d]	**BA21**	2	0	50	37
4	**BA12**	2	0	0	–
5	**BA4**	30	RT	70	17
6	**BA10**	2	0	49	2
7	**BA13**	2	0	40	6
8	**BA15**	24	0	0	–
9	**BA48**	27	RT	58	25
10[e]	**BA50**	27	RT	0	–

[a]All reactions were conducted on a 0.2 mmol scale at RT in toluene (2 mL) with catalyst (5 mol%) without the exclusion of air or moisture.
[b]Isolated yield.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak IC column, 15% IPA/*n*–hexane, 1.0 mL/min, 25 °C.
[d]Reaction conducted with crushed 4 Å MS (100 mg).
[e]Reaction conducted with a catalyst loading of 10 mol%.

the pyrenyl–substituted Brønsted acid **BA49** produced the 1,2–dihydroquinoline in 40% yield and with 6% ee (entry 7). As with **BA12**, the *t*–butylphenyl–substituted catalyst **BA15** was unable to promote allylic amination, leading to no reaction being detected by either TLC analysis or ^{1}H NMR measurements (entry 8). Next, the VAPOL–based phosphoric acid **BA48**–catalysed reaction of **169b** at room temperature for 27 h was found to give the product **171b** in 58% yield and with 25% ee (entry 9). On the other hand, conducting the reaction with 10 mol% of the menthol–based cyclopentadienyl acid catalyst **BA50** was shown to lead to no product formation and the starting material being recovered in near quantitative yield (entry 10).

With the best results, thus far, comprising the use of the Brønsted acid **BA21** under the conditions described in Table 3.2, entry 2, the effect of temperature on this transformation was next explored (Table 3.3). This revealed treatment of the substrate **169b** to 5 mol% of **BA21** in toluene at –40 °C for 4 h led to **171b** being obtained in 62% yield and with 37% ee (entry 1). Repeating the transformation at –78 °C, by

Table 3.3: Examination of the effect of temperature on the asymmetric allylic amination of 1–(2–aminoaryl)prop–2–en–1–ol **169b**.

169b **171b**

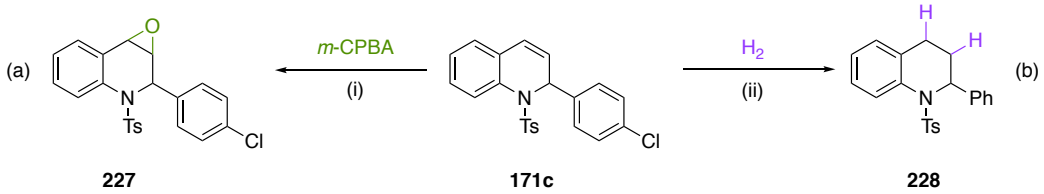
entry[a]	time (h)	temp. (°C)	yield (%)[b]	ee (%)[c]
1	4	–40	62	37
2	10	–78	0	–
3	2	–60 – RT	74	37
4	2	–78 – RT	74	37

[a]All reactions were conducted on a 0.2 mmol scale with **BA21** (5 mol%) at RT in solvent (2 mL) without the exclusion of air or moisture.
[b]Isolated yield.
[c]Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak IC column, 15% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

contrast, resulted in no reaction with only starting material being recovered in near quantitative yield (entry 2). The analogous reaction initiated at –60 °C and allowed to warm up to room temperature over 2 h was found to give **171b** in 74% yield and 37% ee (entry 3). Under similar reaction conditions initiated at –78 °C and allowed to warm up to room temperature, gave a similar product yield of 74% and 37% ee (entry 4). Overall, the results shown in Table 3.2 and Table 3.3 revealed that the cyclisation of 1–(2–aminoaryl)prop–2–en–1–ol **169b** in the presence of 5 mol% of the biphenyl–substituted phosphoramide catalyst **BA21** at 0 °C in toluene was deemed to provide the optimum reaction conditions. Under these reaction conditions, the 1,2–dihydroquinoline **171b** was furnished in 89% yield an ee value of 35%.

3.2.5 Further Functional Group Transformations

To demonstrate the versatility of the racemic 1,2–dihydroquinolines obtained from the present Brønsted acid–mediated cyclisation protocol, their further functional group transformations were investigated (Scheme 3.5). As a first example, treatment of the *N*–heterocycle **171c** in DCM to *m*–CPBA under basic conditions for 6 h was shown to afford the epoxide product **227** in 85% yield. In a second example to illustrate the potential versatility of the compound class, hydrogenation of the 1,2–dihydroquinoline **171c** in the presence of a catalytic amount of Pd/C (10 wt%) and an atmosphere of hydrogen at room temperature for 2 h gave the tetrahydrogenated product **228** in 95% yield.

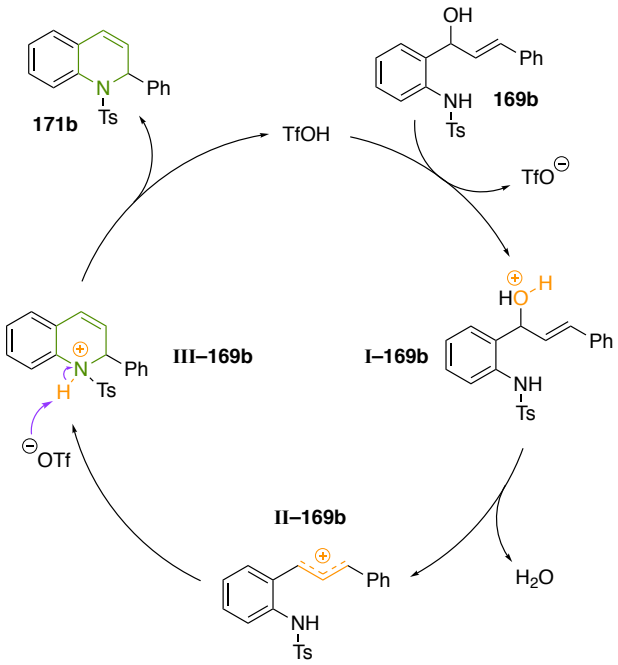


227 **171c** **228**

Scheme 3.5: Modification of **171c**. a) Epoxidation of **171c** to **227**. (i) *m*–CPBA, $NaHCO_3$, DCM, 0 °C, 85% yield;. b) Hydrogenation of **171c** to **228**. (ii) Pd/C (10 wt%), H_2, MeOH, RT, 2 h, 95% yield.

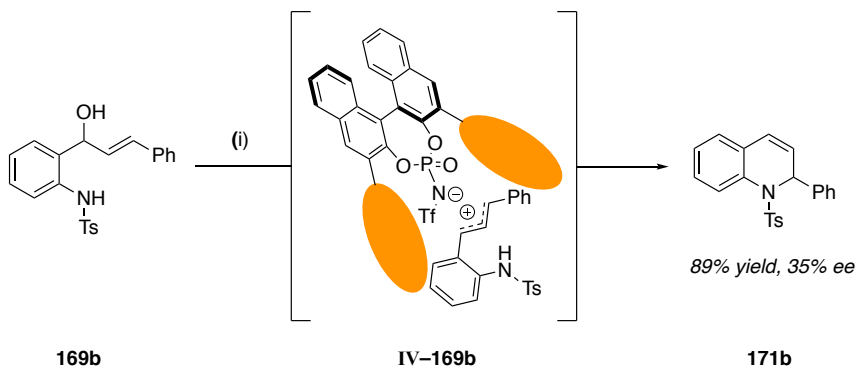
3.2.6 Proposed Reaction Mechanism

A tentative reaction mechanism for the Brønsted acid–catalysed transformation of 1–(2–aminoaryl)prop–2–en–ols to 1,2–dihydroquinolines is shown in Scheme 3.6. It is proposed to proceed in a similar manner to that for the analogous Au(III)–mediated allylic amination reactions.[200] This process could begin with the protonation of the allylic alcohol **169b**, as a representative example, by the Brønsted acid catalyst to form the oxonium species **I–169b**. Subsequent dehydration would afford the allylic carbocation species **II–169b**. Nucleophilic attack of the pendant sulphonamide group onto the allylic cation in **II–169b** would result in cyclisation and formation of the quinolinium intermediate **III–169b**. Deprotonation of this newly formed carbocationic species by the triflate conjugate base would then deliver the desired 1,2–dihydroquinoline product.



Scheme 3.6: Proposed reaction mechanism for the Brønsted acid–mediated conversion of 1–(2–aminoaryl)prop–2–en–1–ol **169b** to 1,2–dihydroquinolines **171b**.

We surmise the moderate product enantioselectivity obtained could be due to the carbocationic intermediate **II–169b** associating with the conjugate base of the chiral Brønsted acid catalyst (Scheme 3.7).[181] This gives the chiral contact ion pair species **IV–169b**. This is further assisted by the possibility of **IV–169b** sitting in a conformation that also allows favourable π–π stacking interactions and potential hydrogen–bonding interactions between the nitrogen–containing functional group and the chiral conjugate base. The moderate enantioselectivity, however, might be due to the formation of an insufficiently intimate ion pair species and/or weakness of the aforementioned stereoelectronic interactions.[196]

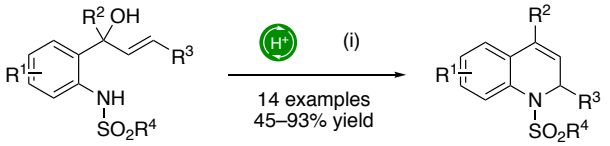


Scheme 3.7: Representation of a contact–ion pair between the Brønsted acid catalyst and a dehydrated cationic intermediate. i) BA21 (5 mol%), PhMe, 0 °C, 2 h, 89% yield, 35% ee. Enantiomeric excess determined using HPLC, conditions: Daicel Chiralpak IC column, 15% IPA/*n*–hexane, 1.0 mL/min, 25 °C.

3.3 Conclusion

In summary, an efficient protocol to access 1,2–dihydroquinolines from 1–(2–aminoaryl)prop–2–en–1–ols that relies on a Brønsted acid–catalysed allylic amination has been presented (Scheme 3.8). The reaction was found to be robust, tolerating a wide variety of substrate substitution patterns, and complimenting the metal–catalysed version of this transformation. The effectiveness of the present operationally simple synthetic protocol was demonstrated by the good to excellent product yields obtained

with a low catalyst loading of 0.01 mol%. The protocol was also shown to be selective with no evidence of products arising from Friedel–Crafts reactions, dehydration processes, or competitive hydroaminations observed. This is notable given the need for more expedient and direct atom–economical method that can utilise low–cost and readily available reagents and catalysts.



169 171

Scheme 3.8: A Brønsted acid-mediated cyclisation protocol as an efficient approach to 1,2–dihydroquinoline 171 derivatives from 1–(2–aminoaryl)prop–2–en–1–ols 169. (i) TfOH (0.01 mol%), PhMe, air, RT.

Chapter 4

4.0 Brønsted Acid–Catalysed Cyclisation of *β*–Amino–1,4–enols to Oxazol–2(3*H*) –ones and 5–Alkenyloxazolidin–2–ones

4.1 Introduction

Oxazolidinone–containing compounds are immensely important targets in organic chemistry and have, over the years, received a significant amount of attention due to their biological significance and versatility in organic synthesis as a ligand and intermediate (Figure 4.1).[201–215] A prominent example is the development of the oxazolidinone–containing linezolid **229** marketed as Zyvox®, one of only three new antibiotic drug classes approved by the Food and Drug Administration in the last

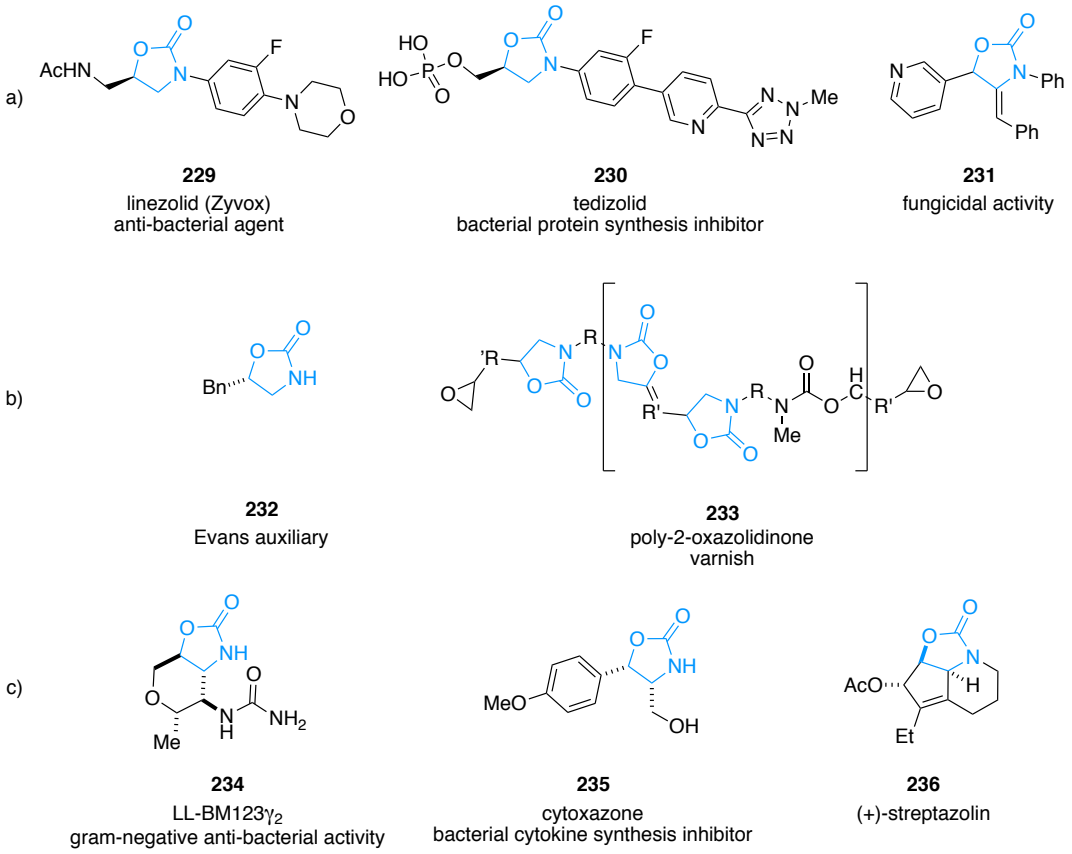
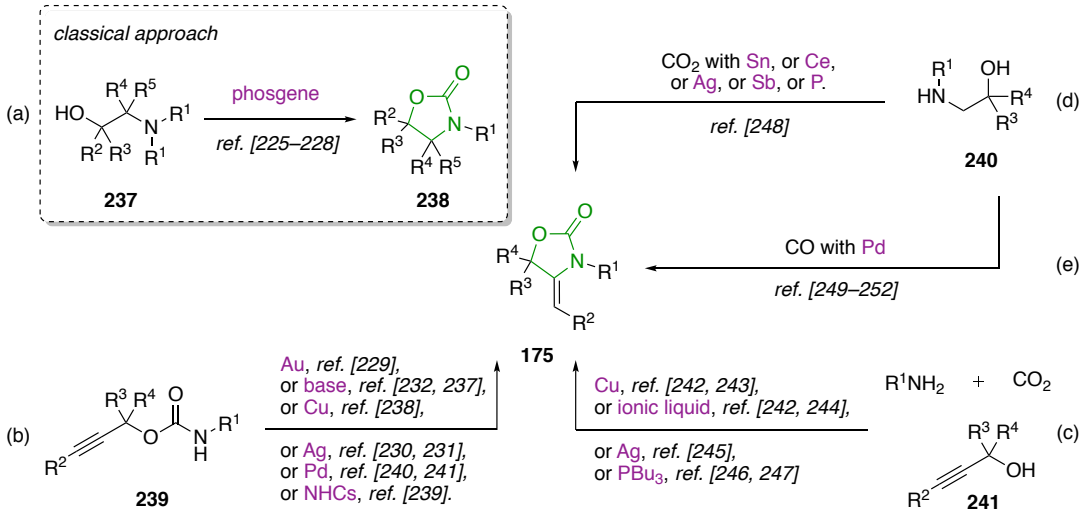


Figure 4.1: a) Selected pharmacologically relevant oxazolidinones. b) Selected functional molecules featuring the oxazolidinone core structure. c) Selected oxazolidinone derivatives featured in natural products.

thirty years.[216] Linezolid is an antibiotic treatment for drug–resistant, gram–positive bacterial infections in strains such as *Streptococci* and *Enterococci*, for use particularly when other antibiotics have failed to perform.[217,218] Other pharmaceutical compounds include tedizolid **230**, a bacterial protein synthesis inhibitor, and the pyridyl–substituted antifungal oxazolidinone **231**.[204] Oxazolidinones such as the benzyl–substituted adduct **232** developed by Evans and co–worker have also been shown to be versatile chiral auxiliaries in a range of asymmetric reactions.[219,220] The *O*,*N*–heterocyclic ring system features heavily in polymerised materials such as the poly–2–oxazolidinone varnish **233** as well as in various other applications from tablet coatings, lubricant additives, dye assistants, to rust inhibitors.[221,222] Natural products containing the oxazolidinone structure include LL–BM123γ_2 **234**, a gram–negative antibacterial agent,[223] cytoxazone **235**, a bacterial cytokine synthesis inhibitor,[204] and (+)–streptazolin **236**, a natural product isolated from the bacterium *Streptomyces viridochromogenes*.[224] This versatility of the oxazolidinone ring system has led to a plethora of methods for their construction (Scheme 4.1).

Typically, access to this compound class has employed phosgene or chloroformate as carbonyl precursors (Scheme 4.1a).[225–228] In addition, the cyclisation of propargylic carbamates **239** have been extensively explored and shown to proceed with a range of catalysts such as Au,[229] Ag,[230,231] Brønsted base,[232,237] Cu,[238] NHCs,[239] and Pd (Scheme 4.1b).[240,241] As a carbonyl surrogate, CO_2 has been utilised with propargyl alcohols **241** in conjunction with amines to afford oxazolidinones in the presence of Cu,[242,243] ionic liquids,[242,244] Ag,[245] and phosphines (Scheme 4.1c).[246,247] The utility of CO_2 to generate the heterocycle from amino alcohols **240** has also been demonstrated in the presence of Sn, Ce, Ag, Sb, alkali metals, and phosphorous electrophiles

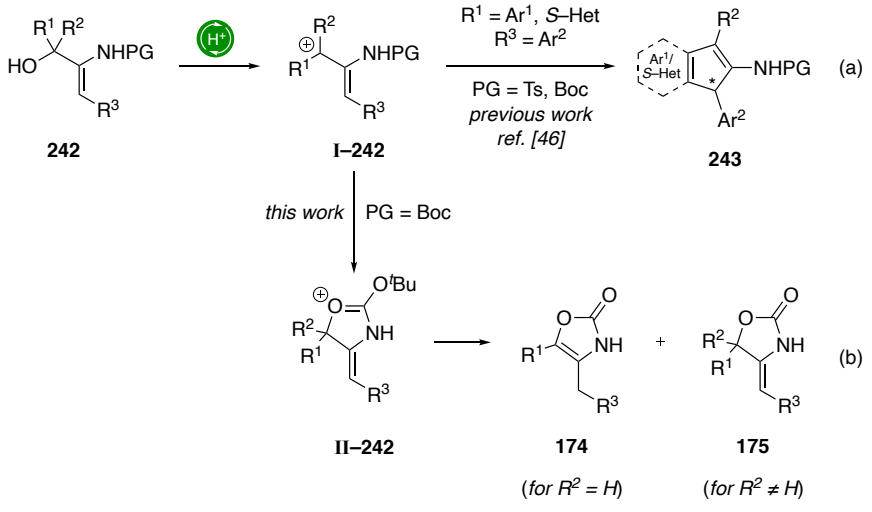


Scheme 4.1: Reported methods for the generation of the 2–oxazolidinone ring.

(Scheme 4.1d).[248] Added to this have been Pd–mediated synthetic methods that make use of amino alcohols with CO to produce the oxazolidinone adduct (Scheme 4.1e).[249–252] All these synthetic methods, however, often require the presence of metal salts and the use of high reaction temperatures and pressures. Other limitations include poor solubility of the reagents, high catalyst loadings, long reaction times, and expensive and/or toxic catalysts. For these reasons, the development of novel, efficient, and low–cost synthetic protocols continue to be pursued in organic chemistry.[239a]

In this regard, we queried whether a Brønsted acid–catalysed synthetic method could be realised to assemble the *O*,*N*–heterocyclic ring system. In recent years, a growing number of reports have shown the utility of a broad range of π–rich alcohols as starting materials in Brønsted acid–mediated C–C bond formation protocols.[253] This has included synthetic methods that direct the intermediate carbocationic species, produced under such acidic reaction conditions, to engage in cyclisation pathways to furnish cyclic compounds of potential synthetic value.[254] An example of this is the enantioselective asymmetric *N*–triflyl phosphoramide–mediated dehydrative Nazarov–type electrocyclisation to 1*H*–indenes and 4*H*–cyclopenta[*b*]thiophenes

from electron–rich aryl and 2–thienyl vinyl *β*–amino alcohols (Scheme 4.2a).[256] Building on these developments, we queried the potential for intercepting the expected carbocationic intermediate **I–242** by a pendant *t*–butyl carbamate group (*N*–Boc) rather than a dehydrative electrocyclization (Scheme 4.2b). We envisioned that, by fine–tuning the reaction conditions, we could achieve this aim by promoting the simultaneous decomposition of the *N*–protecting group and the dehydration of the carbinol alcohol to provide the reputed carbonic acid species **II–242**. This ensuing carbocationic species could subsequently participate in a cyclisation pathway commencing with addition of the carbonyl oxygen centre to the allylic carbocation to deliver either the oxazol–2(3*H*)–one **174**, or the 5–alkenyloxazolidin–2–one **175** when R^1, $R^2 \neq H$. In this chapter, we describe our development of this chemistry that provides a practical synthetic method to access these two members of the *O*,*N*–heterocyclic compound class from electron–rich secondary and tertiary aryl vinyl *β*–amino alcohols under mild atmospheric conditions.

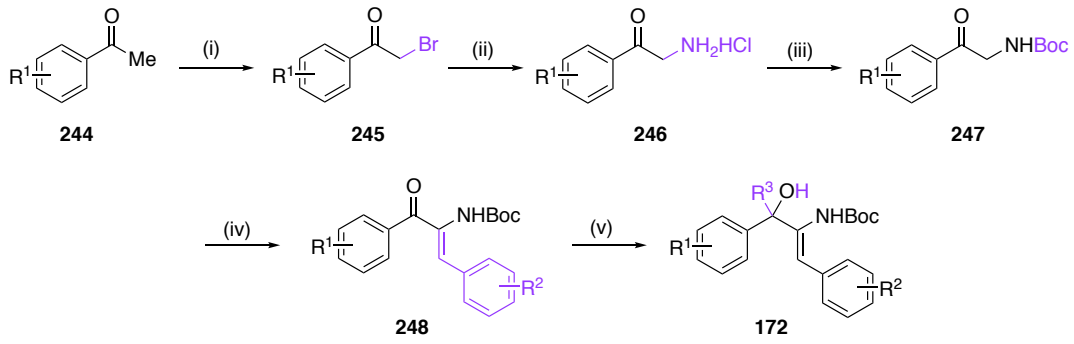


Scheme 4.2: Brønsted acid–catalysed reactivities of *β*–amino–1,4–enols.

4.2 Results and Discussion

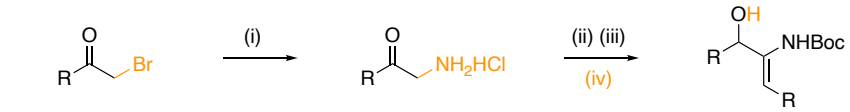
4.2.1 The Synthesis of the Starting Materials

All *N*–Boc amino alcohols **172** examined in the present work were prepared following known experimental procedures (Scheme 4.3).[269] The synthetic route involved initial α–bromination of acetophenone **244** to afford the α–bromoketone **245**. After recrystallisation, this substrate was subjected to amination conditions with hexamethylenetetramine followed by acid–mediated hydrolysis to afford the ammonium salt **246**. For compounds where R^1 = *p*–OMe, treatment of the ammonium salt with di–*t*–butyl dicarbonate under basic conditions gave the *N*–Boc ketone **247** in 68% yield. Subjecting the acetamide **247** to aldol condensation with the appropriate aldehyde afforded the desired α,β–unsaturated ketone **248**. Subsequent $NaBH_4$–mediated reduction of the carbonyl compound provided access to the secondary allylic alcohol substrate **172** in 62% yield over two steps. Alternatively, Grignard addition of *p*–methoxyphenylmagnesium bromide to **248** produced the tertiary allylic alcohol substrate in 71% yield over two steps.



Scheme 4.3: Synthesis of *N*–Boc amino alcohols **172** from the appropriate acetophenones. R^1, R^2 = H, R^3 = H or Me. i) NBS (1.15 eq.), *p*–TsOH (10 mol%), MeCN; or Br_2 (1 eq.), DCM, <3 °C. ii) Hexamethylenetetramine (1.1 eq.), $CHCl_3$, 60 °C, then conc. HCl, EtOH. iii) Boc_2O (1.5 eq.), Na_2CO_3 (1.5 eq.), DCM, 68% yield over three steps. iv) RCHO (1.2 eq.), piperidine (10 mol%), propionic acid (20 mol%), PhMe. v) $NaBH_4$ (3 eq.), EtOH, 0 °C–RT, 62% yield over two steps; or R^3MgX (4.5 eq.), THF, –78 °C–RT, 71% yield over two steps.

The synthetic route outlined in Scheme 4.3, however, was found to be incompatible for the preparation of certain substrates (Scheme 4.4). When treated with 1.1 equivalents of hexamethylenetetramine in chloroform, the α–bromoketones **245w** and **245x** failed to afford the desired ammonium salts **246w** and **246x**. Similarly, the analogous reactions with heteroaryl α–bromoketones **245**α–γ were also unable to furnish the corresponding ammonium hydrochloride salts **246**α–γ. It was also found that the ketone precursors to the desired β–amino–1,4–enols **172y** and **172z** were unable to withstand the reducing conditions outlined in Scheme 4.4. As a result, only a mixture of unidentifiable decomposition products was produced as determined by ^{1}H NMR measurements of the crude reaction mixtures.



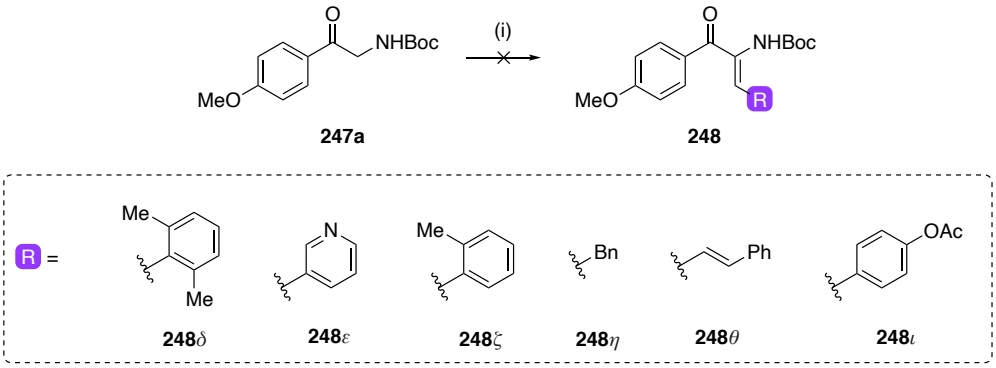
245w (R = cyclopropyl)
245x (R = cyclohexyl)
245y (R = 2-furyl)
245z (R = 2-thienyl)
245α (R = 3-methylphenyl)
245β (R = 4-ethylphenyl)
245γ (R = 5-benzo[*d*][1,3]dioxole)

246w (R = cyclopropyl, 0%)
246x (R = cyclohexyl, 0%)
246y (R = 2-furyl, 86%)
246z (R = 2-thienyl, 79%)
246α (R = 3-methylphenyl, 0%)
246β (R = 4-ethylphenyl, 0%)
246γ (R = 5-benzo[*d*][1,3]dioxole, 0%)

172y (R = 2-furyl, 0%)
172z (R = 2-thienyl, 0%)

Scheme 4.4: Synthesis of secondary β–amino–1,4–enols **172**. i) Hexamine (1.1 eq.), $CHCl_3$, 60 °C, then conc. HCl, EtOH. ii) Boc_2O (1.5 eq.), Na_2CO_3 (1.5 eq.), DCM. iii) RCHO (1.2 eq.), piperidine (10 mol%), propionic acid (20 mol%), PhMe. iv) $NaBH_4$ (3 eq.), EtOH, 0 °C–RT.

The synthesis of a further set of substrates **248**δ–ι derived from the aldol condensation of the *N*–Boc–protected ketone **247a** with the appropriate aldehydes was found to be unsuccessful (Scheme 4.5). In each case, only a mixture of the starting materials or unidentifiable decomposition products were produced as determined by ^{1}H NMR measurements of the crude reaction mixtures.

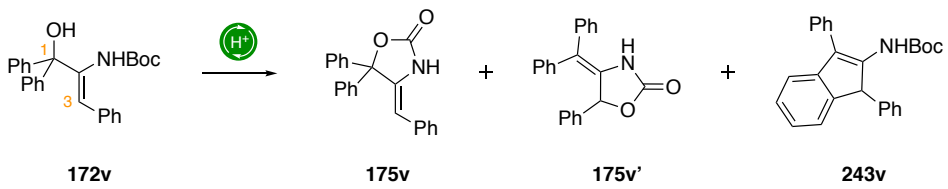


Scheme 4.5: Unsuccessful synthesis of *N*–Boc α,β–unsaturated ketones **248**. (i) RCHO (1.2 eq.), piperidine (10 mol%), propionic acid (20 mol%), PhMe.

4.2.2 Preliminary Studies

To test the feasibility of our hypothesis, the Brønsted acid–catalysed cyclisations of alcohol **172v**, selected as the model substrate, were investigated to determine the optimum reaction conditions (Table 4.1). Subjecting the substrate to 5 mol% of TfOH in DCE at room temperature for 1 h gave the two oxazolidinone positional

Table 4.1: Summary of the initial screening of conditions of the Brønsted acid–catalysed cyclisation of 172v.



172v **175v** **175v'** **243v**

entry[a]	temp. (°C)	yield (%)[b]		
		175v	**175v'**	**243v**
1	RT	29	21	19
2	–40	–[c]	–	–
3	–78	–[c]	–	–
4	70	38	28	5

[a]All reactions were conducted on a 0.2 mmol scale in DCE (2 mL) with TfOH (5 mol%) for 1 h without the exclusion of air or moisture.
[b]Isolated yield.
[c]Unknown mixture of decomposition products based on ^{1}H NMR analysis of the crude reaction mixture.

isomers **175v** and **175v'**, and the indene **243v** in respective yields of 29, 21, and 20% yield (entry 1). The structure of the *O*,*N*–heterocycle **175v** was unambiguously determined by X–ray crystallographic analysis (Figure 4.2). To explore whether reaction temperature might provide a greater degree of chemoselective control, the experiment was next conducted at –40 °C, –78 °C, and 70 °C (entries 2–4). At –40 °C and –78 °C, this gave a mixture of unknown decomposition products in both cases, as determined by ^{1}H NMR analysis of the crude reaction mixtures. The analogous reaction at 70 °C, on the other hand, afforded the three products **175v**, **175v'**, and **243v** in 38, 28, and 5% yield, respectively. We postulate that the furnished oxazolidinones **175v** and **175v'** could be due to competitive C–C bond formation at C1 and C3 in the premised carbocation intermediate. Indene **243v** could result from an alternative competitive pathway involving 4π–electrocyclization on formation of the same proposed carbocationic intermediate.[46] Deducing that the high degree of resonance

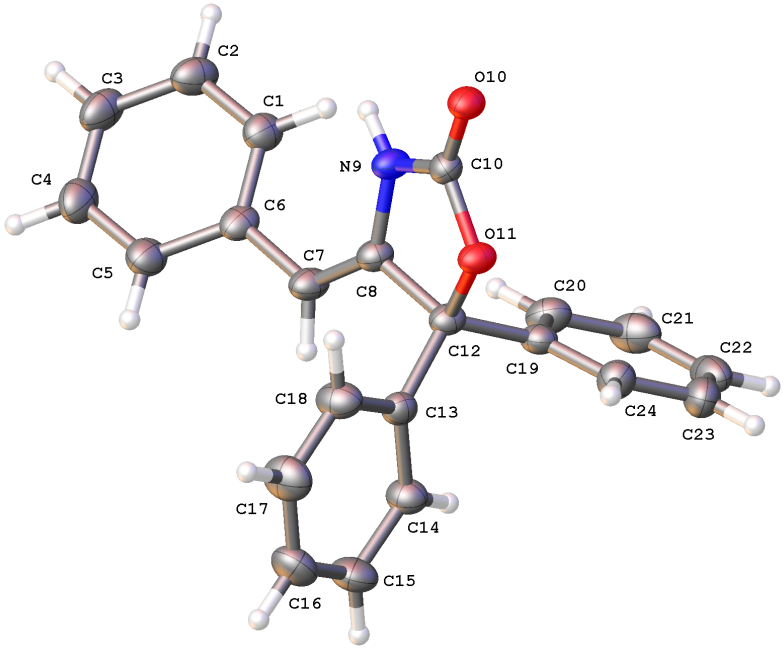
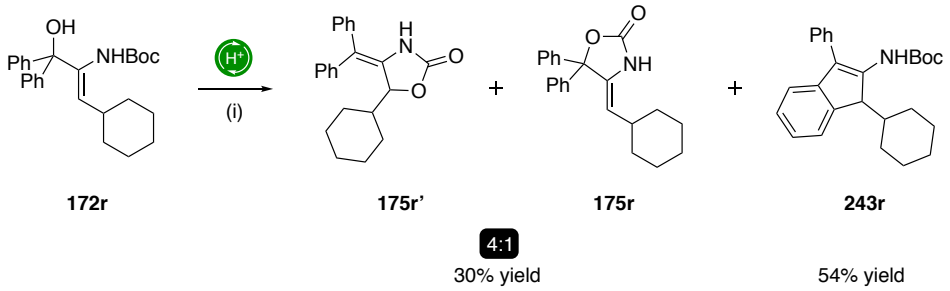


Figure 4.2: ORTEP drawing of 4–(cyclohexylmethylene)–5,5–diphenyloxazolidin–2–one **175v** with thermal ellipsoids at 50% probability levels.[271]

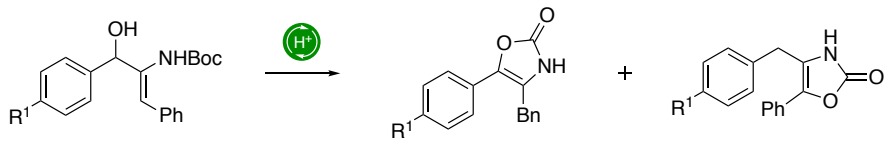
stabilisation of the carbocation species to be a possible cause for the poor product selectivity, we surmised that substrates where these electronic interactions were less pronounced might provide a solution to improve chemoselectivity. With this in mind, the cyclohexyl–substituted alcohol **172r** was chosen and subjected to 5 mol% of TfOH in DCE at room temperature for 1h (Scheme 4.6). Under these reaction conditions, a 4:1 inseparable mixture of the oxazolidin–2–one positional isomers **175r'** and **175r** in 30% yield was obtained. It additionally provided the indene **243r** in 54% yield.



Scheme 4.6: Brønsted acid–catalysed reaction of alcohol **172r**. i) TfOH (5 mol%), DCE, RT, 1 h.

Attention was next turned to the TfOH–mediated reaction of secondary *β*–amino–1,4–enol substrates **172l**–**m** in which resonance stabilisation might be further reduced due to the presence of only one aromatic group (Table 4.2). Exposing 0.2 mmol of the *p*–tolyl–substituted substrate **172l** to TfOH (5 mol%) in DCE at room temperature for 1 h afforded the oxazol–2(3*H*)–ones **174l** and **174l'** in 66 and 13% yield, respectively (entry 1). The indene adduct was not detected by ^{1}H NMR spectroscopic measurements. Repeating the reaction with the *p*–anisyl–substituted alcohol **172b** gave a similar outcome, providing **174b** and **174b'** in 51 and 23% yield, respectively (entry 2). The analogous reaction with the phenyl–substituted substrate **172m** was found to provide **174m** as the only product in 42% yield (entry 3).

Table 4.2: Summary of the Brønsted acid–catalysed cyclisation of secondary alcohol substrates **172.**



172 **174** **174'**

entry[a]	substrate	R^1	yield (%)[b]	
			174	**174'**
1	l	Me	66	13
2	b	OMe	51	23
3	m	H	42	–

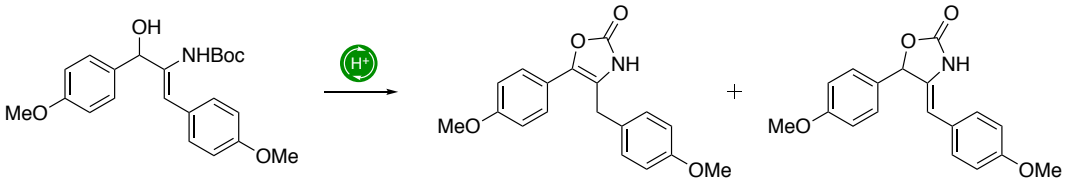
[a]All reactions were conducted on a 0.2 mmol scale in DCE (2 mL) with TfOH (5 mol%) at RT for 1 h without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.

4.2.3 Optimisation of the Reaction Conditions

With these preliminary results in hand, a determination of the optimum reaction conditions for the Brønsted acid–catalysed cyclisation was conducted with the secondary *β*–amino–1,4–enol **172a** as the model substrate (Table 4.3). This study initially revealed that exposing alcohol **172a** to *p*–TsOH (5 mol%) in EtOAc at room temperature under atmospheric conditions for 48 h provided the oxazol–2(3*H*)–one **174a** and oxazolidine–2–one **175a** in 22 and 25% yield, respectively (entry 1). Repeating the reaction in EtOH afforded the two *O*,*N*– heterocyclic products in yields of 13 and 21% (entry 2). In contrast, treating the *N*–Boc protected alcohol **172a** with TFA or benzoic acid in place of TfOH was found to result in no reaction observed by either TLC analysis or ^{1}H NMR measurements of the crude reaction mixtures (entries 3 and 4). Our subsequent studies found that the reaction mediated by TfOH in DCM furnished **174a** and **175a** in yields of 59 and 12%, respectively (entry 5). The analogous reaction conducted in Et_2O instead of DCM as the solvent afforded **174a**

and **175a** in yields of 12 and 33%, respectively (entry 6). Similarly, employing THF as the reaction solvent was shown to give **174a** and **175a** in respective yields of 38 and 39% (entry 7). Changing the reaction medium to EtOAc as solvent was found to give a similar outcome, providing **174a** and **175a** in yields of 35 and 22%, respectively (entry 8). With 1,2–dichloroethane as the solvent, the oxazol–2(3*H*)–one and oxazolidin–2–one adducts were furnished in respective yields of 46 and 9% (entry 9).

Table 4.3: Optimisation of the reaction conditions for the Brønsted acid–catalysed cyclisation of **172a**.



172a **174a** **175a**

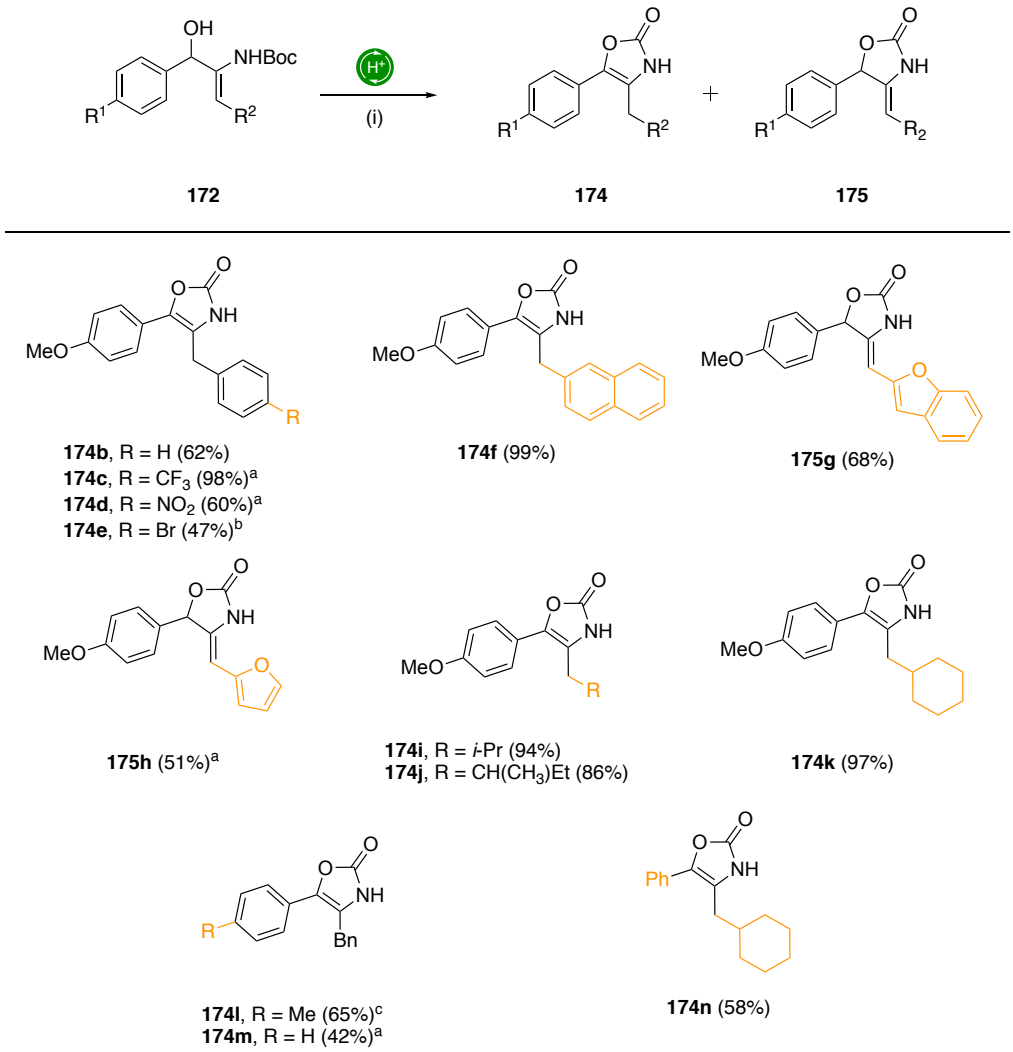
entry[a]	catalyst	solvent	yield (%)[b]	
			174a	**175a**
1	*p*–TsOH	EtOAc	22	25
2	*p*–TsOH	EtOH	13	21
3	TFA	–[c]	–[d]	–
4	$PhCO_2H$	–[c]	–[d]	–
5	TfOH	DCM	59	12
6	TfOH	Et_2O	12	33
7	TfOH	THF	38[d]	39[d]
8	TfOH	EtOAc	35	22
9	TfOH	DCE	46	9
10	TfOH	$(CH_3)_2CO$	27	30
11	TfOH	EtOH	60[e]	–
12[f]	TfOH	EtOH	59[e]	–

[a]All reactions were conducted on a 0.1 mmol scale in solvent (1 mL) with catalyst (5 mol%) at RT for 48 h without the exclusion of air or moisture.
[b]^{1}H NMR yield determined with CH_2Br_2 as the internal standard.
[c]Reaction conducted in DCM, Et_2O, THF, EtOAc, DCE, $(CH_3)_2O$, and EtOH.
[d]No reaction observed with TLC analysis or ^{1}H NMR measurements of the crude reaction mixtures.
[e]Isolated yield.
[f]Reaction conducted at reflux for 1 h.

Likewise, the analogous reaction in acetone was found to lead to **174a** and **175a** being attained in 27 and 30% yield, respectively (entry 10). In a final set of control reactions with EtOH as the solvent, the oxazol–2(3*H*)–one **174a** was obtained as the only product in 60% yield (entry 11). A comparable product yield of 59% was afforded when the experiment was conducted for a second time at reflux temperature for 1 h, which was then deemed to provide the optimum reaction conditions (entry 12).

4.2.4 Determining the Scope of the Catalytic Method

To assess the scope of the present synthetic approach, our attention first turned to the reactions of a series of secondary *β*-amino-1,4-enols (Scheme 4.7). In general, the cyclisation of starting alcohols **172b–f** and **172i–n** revealed the Brønsted acid–catalysed reaction conditions to be wide–ranging, affording the corresponding oxazol–2(3*H*)–ones in 42–99% yield. Experiments with diaryl–containing starting materials featuring either electron–withdrawing or –donating moieties in the *para*–position of the aromatic rings (**172b–d** and **172f**) were demonstrated to cyclise to give **174b–d** and **174f** in 60–99% yield. The conversion of the five–membered heterocycle **174b** to the *N*–tosyl–protected derivative *N*–Ts–**174b** enabled the structure of the *O*,*N*–heterocycle to be unambiguously determined by X–ray crystallographic analysis (Figure 4.3). Starting materials featuring an alkyl (**172i,j**) or cyclohexyl (**172k**) motif instead of an aryl group at the enamine carbon centre were found to afford the cyclic adducts **174i–k** in 86–97% yield. A comparable outcome was found for *β*–amino–1,4–enols featuring a *para*–tolyl and benzyl (**172l**) or phenyl and benzyl (**172m**) or cyclohexyl (**172n**) motifs at the carbinol– and enamine–carbon centres, respectively. In these transformations, the corresponding oxazol–2(3*H*)–ones **174l–m** were furnished in 42–65% yield with **174l** also afforded as an inseparable mixture of positional isomers in a ratio of 10:1. On the other hand, the analogous reactions of *p*–



Scheme 4.7: Brønsted acid–catalysed cyclisations of various secondary β–amino–1,4–enols. i) TfOH (5 mol%), EtOH, reflux, 0.25–1 h. [a]Reaction conducted in 1,2–dichloroethane as the solvent. [b]Product was obtained as a separable mixture of 174e and 175e in an overall yield of 68% and a ratio = 2.2:1 with compound 175e isolated in 21% yield. [c]Product was obtained as an inseparable mixture of positional isomers in a ratio = 10:1.

anisyl–containing starting materials with a *p*–bromophenyl (**172e**), 2–benzofuranyl (**172g**), or 2–furanyl (**172h**) moiety at the enamine carbon centre were revealed to be the exception. In the case of the latter two substrates, the oxazolidine–2–ones **175g** and **175h** furnished as were the only products with respective yields of 68 and 51%. For the cyclisation of **172e**, a separable mixture of both the oxazolidine–2–one **175e** and the oxazol–2(3*H*)–one **174e** was obtained in 21 and 26% yield, respectively.

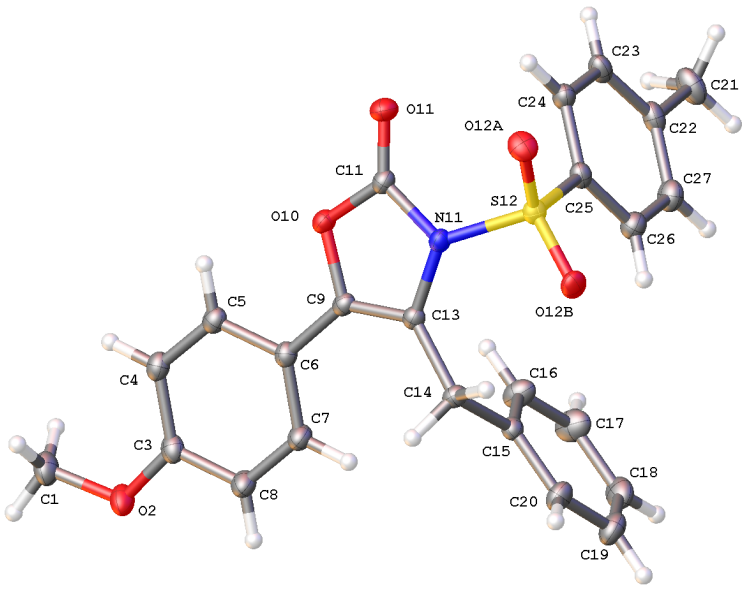
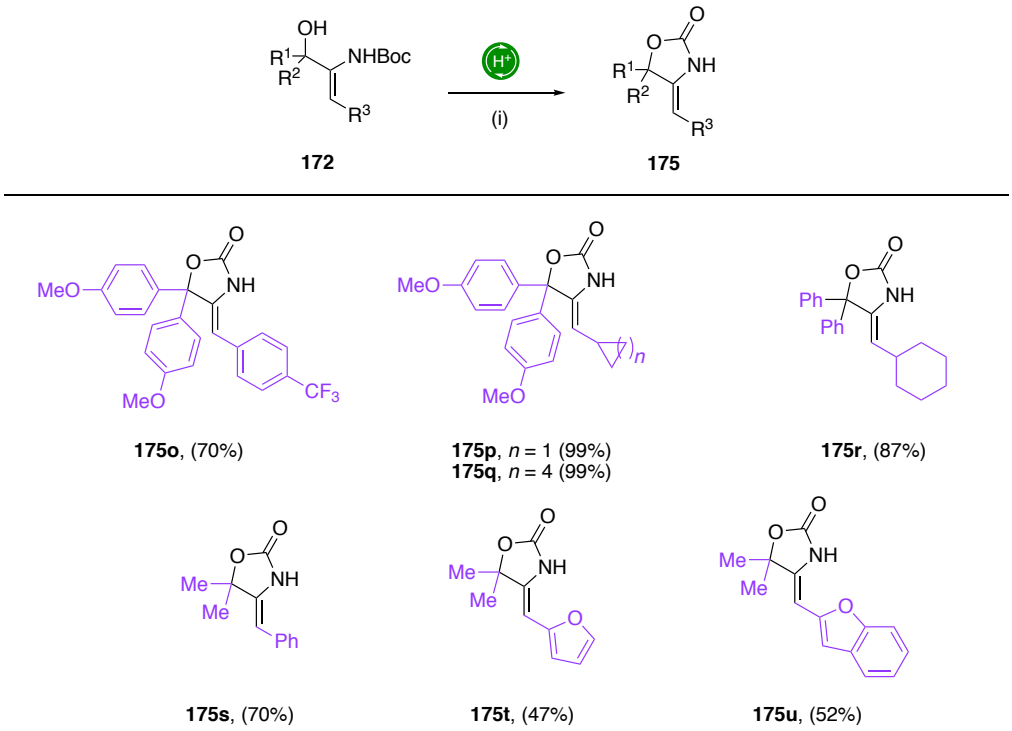


Figure 4.3: ORTEP drawing of 4–benzylidene–5–(4–methoxyphenyl)–3–tosyloxazolidin–2–one *N*–Ts–**174b** with thermal ellipsoids at 50% probability levels.[271]

To further assess the generality of the present Brønsted acid–mediated procedure, the cyclisation of various tertiary *β*–amino–1,4–enols was next examined (Scheme 4.8). This initially revealed that substrates possessing geminal di–*p*–anisyl motifs at the carbinol carbon centre in conjunction with a *p*–(trifluoromethyl)phenyl (**172o**) or cycloalkyl (**172p** and **172q**) motif gave the appropriate five–membered heterocycle **175o–q** in yields of 70–99%. Under the optimised TfOH–mediated reaction conditions, the cyclisation of **172r**, featuring geminal diphenyl motifs and a cyclohexyl group at the respective carbinol carbon and enamine carbon centres, provided the corresponding oxazolidin–2–one **175r** in 87% yield. The structure of the *O*,*N*–heterocycle was unambiguously confirmed by X–ray crystallographic analysis (Figure 4.4). Likewise, starting alcohols containing *gem*–dimethyl groups at the carbinol carbon centre and a phenyl (**172s**), 2–furyl (**172t**), or 2–benzofuryl (**172u**) at the enamine carbon centre afforded the appropriate five–membered heterocyclic adducts **175s–u** in yields of 70, 47, and 57%, respectively.



Scheme 4.8: Brønsted acid–catalysed cyclisations of various tertiary β–amino–1,4–enols **172**. i) TfOH (5 mol%), EtOH, reflux, 0.25–1 h.

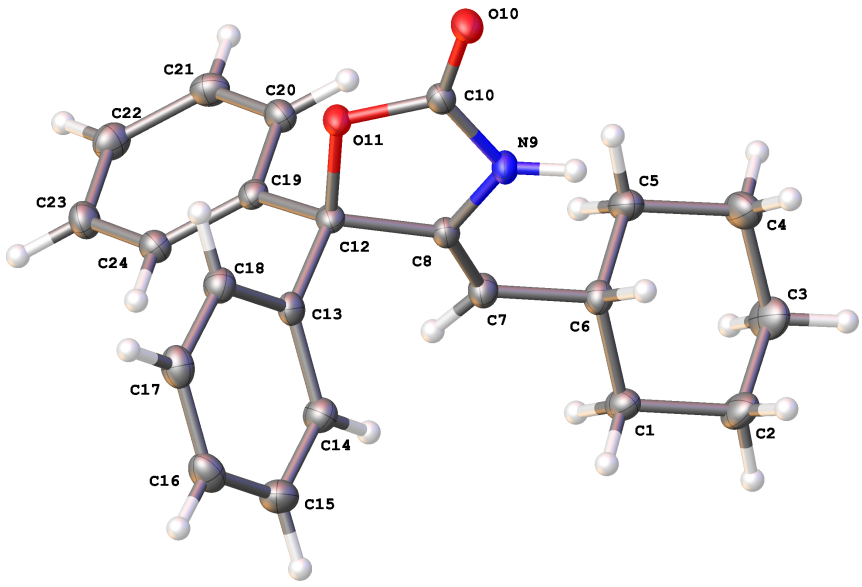


Figure 4.4: ORTEP drawing of 4–benzylidene–5,5–diphenyloxazolidin–2–one **175r** with thermal ellipsoids at 50% probability levels.[271]

4.2.5 Proposed Reaction Mechanism

In view of the results obtained and previous work, a postulated Brønsted acid–catalysed reaction mechanism is illustrated in Figure 4.5.[46] This process might begin with Brønsted acid–mediated protonation of the carbinol oxygen centre of the amino alcohol **172** to generate the protonated species **I–172**. This intermediate may then undergo dehydration to generate the carbocationic species **II–172**. Subsequent cyclisation through addition of the carbonyl oxygen centre to the allylic carbocation motif in **II–172** to deliver the five–membered oxonium adduct **III–172**. Elimination of the *tert*–butyl motif in the form of isoprene *via* deprotonation of one of the methyl groups would then produce the oxazolidin–2–one **175**. For substrates where R^2 = H, a further step involving isomerisation of the *O*,*N*–heterocycle would afford the more stable oxazol–2(3*H*)–one **174**. Although the reason for the generation of both **174d** and **175d** remains unclear, the favoured formation of **175f** and **175g** could be due to the potential for H–bonding between the amino group of the cyclic carbamate

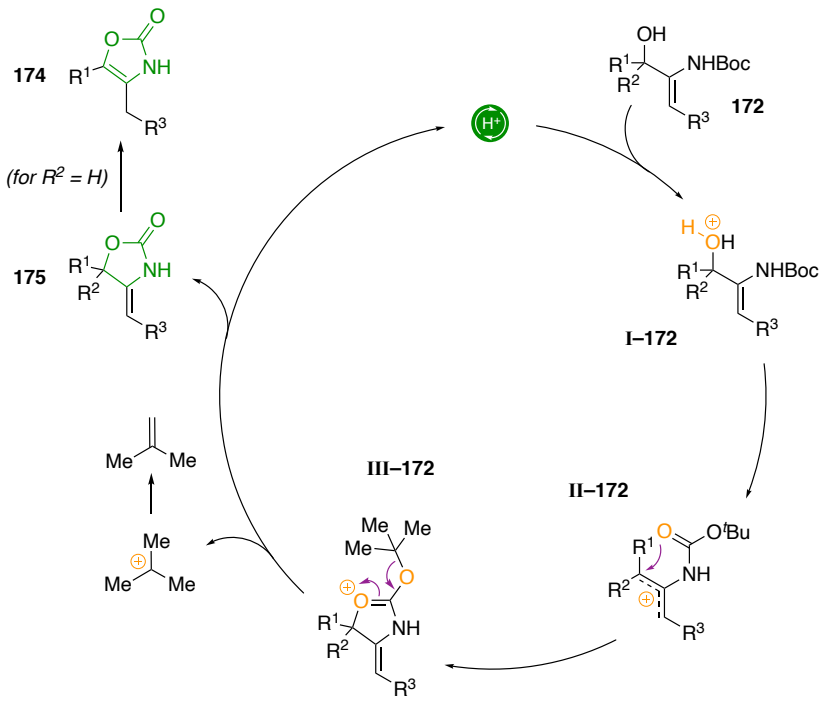
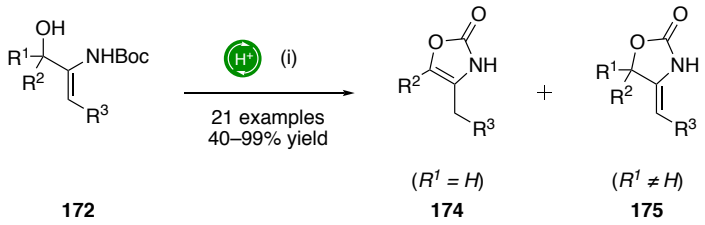


Figure 4.5: Proposed mechanism for the cyclisation of *β*–amino–1,4–enols mediated by TfOH.

and the oxygen centre of the *O*–heterocycle in these compounds. This H–bonding has the potential to hinder the isomerisation of these adducts to their corresponding oxazol–2(3*H*)–ones **174f** and **174g**.

4.3 Conclusion

In summary, a Brønsted acid–mediated method for the efficient cyclisation of secondary *β*–amino–1,4–enols to oxazol–2(3*H*)–ones **174** has been developed (Scheme 4.9). The synthetic protocol was also shown to be applicable to the cyclisation of tertiary alcohols to give the corresponding 5–alkenyloxazolidin–2–ones **175**. This transformation has been achieved without the need to exclude air or moisture and was demonstrated to be applicable to substrates containing a wide variety of substitution patterns. The synthetic approach compliments the analogous transition metal–catalysed transformations to these two members of the five–membered *O*,*N*–heterocyclic family of compounds.

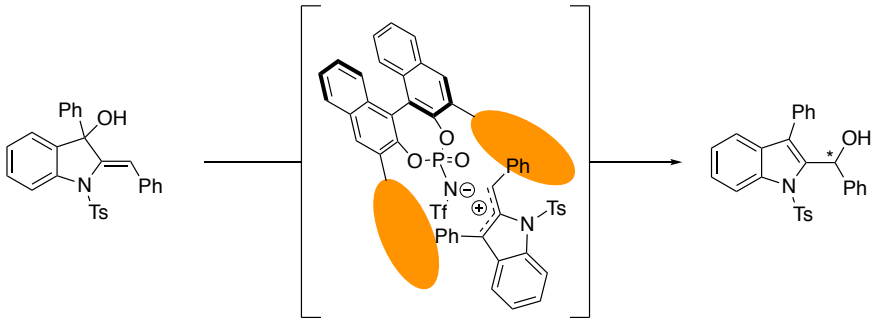


Scheme 4.9: A Brønsted acid–mediated cyclisation protocol as an efficient approach to oxazol–2(3*H*)–one **174** and 5–alkenyloxazolidin–2–one **175** derivatives from the respective secondary and tertiary *β*–amino–1,4–enols. (i) TfOH (5 mol%), EtOH, air, reflux, 0.25–1 h.

Chapter 5

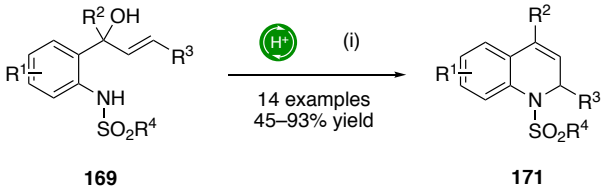
5.0 Concluding Remarks

In summary, this thesis has explored new reactivities of alcohols as pro–electrophiles in the field of Brønsted acid catalysis. In Chapter 2, the efforts towards realising the first asymmetric 1,3–allylic alcohol isomerisation of 3–indolinols to 2–indolyl methanols was discussed (Scheme 5.1). A broad selection of chiral Brønsted acid catalysts were screened during the investigation into defining the optimum enantioselective reactions conditions, and although excellent yields and short reaction times were achieved, the asymmetric 1,3–AAI was unable to provide indolyl methanols in a highly enantioselective manner. It was proposed that the asymmetric Brønsted acid catalysts employed in this study were unable to form a sufficiently intimate contact ion pair transition state for the transfer of stereochemical information from the catalyst anion to the substrate carbocation.



Scheme 5.1: Chiral Brønsted acid–mediated 1,3–AAI of 3–indolinols 166b to 2–indolyl methanols 168b.

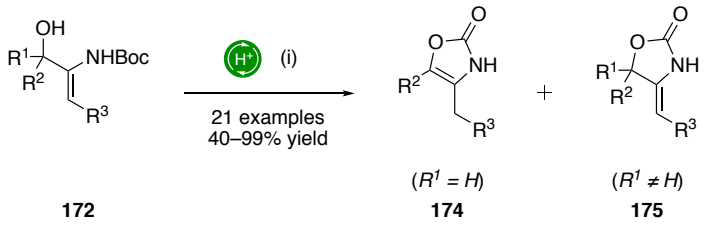
In Chapter 3, the development of a Brønsted acid–mediated allylic amination to access 1,2–dihydroquinolines from 1–(2–aminoaryl)prop–2–en–1–ols was discussed (Scheme 5.2). This was achieved with an operationally simple and efficient synthetic protocol that employed TfOH at a low catalyst loading of 0.01 mol% under ambient conditions. This method was shown to be robust, tolerating a variety of substrate substitution patterns, and providing good to excellent products yields.



169 **171**

Scheme 5.2: A Brønsted acid-mediated cyclisation protocol as an efficient approach to 1,2–dihydroquinoline **171** derivatives from 1–(2–aminoaryl)prop–2–en–1–ols **169**. (i) TfOH (0.01 mol%), PhMe, air, RT.

In Chapter 4, the Brønsted acid–catalysed cyclisation of *β*–amino–1,4–enols **172** as a new synthetic strategy to the oxazol–2(3*H*)–ones **174** and 5–alkenyloxazolidin–2–ones **175** was discussed (Scheme 5.3). This dehydrative process was accomplished without the need to exclude air or moisture and was shown to tolerate a variety of substrate substitution patterns to provide these *O*,*N*–heterocycles in good to excellent yields.



172 (*R*¹ = *H*) **174** (*R*¹ ≠ *H*) **175**

Scheme 5.3: A Brønsted acid–mediated cyclisation protocol as an efficient approach to oxazol–2(3*H*)–one **174** and 5–alkenyloxazolidin–2–one **175** derivatives from the respective secondary and tertiary *β*–amino–1,4–enols. (i) TfOH (5 mol%), EtOH, air, reflux, 0.25–1 h.

Chapter 6

6.0 Experimental

6.1 General Information

^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were measured on a Bruker Avance 300, 400, 500, or 600 MHz spectrometers at room temperature (298 K). Chemical shifts (δ) are recorded in parts per million (ppm) relative to solvent residual peaks ($CDCl_3$ ∂H: 7.26, δC: 77.16; CD_2Cl_2 δH: 5.32, δC: 53.84; d6-acetone δH: 2.05, δC: 206.26, 29.84; d6-DMSO δH: 2.50, δC: 39.52). Couplings constants (J) are recorded in Hertz and are reported to the nearest 0.5 Hz. ^{1}H and ^{13}C assignments are based on the assessment of COSY, APT, HSQC, and HMBC correlations. Multiplicities are given as: multiplet (m), singlet (s), broad singlet (brs), doublet (d), triplet (t), quartet (q), quintet (quint.), sextet (sext.), heptet (hept.), or the appropriate combination, e.g: dt = doublet of triplets.

Low resolution mass spectra were determined on an Agilent Technologies 6130 Quadrupole LC-MS mass spectrometer. HRMS were obtained on a Bruker MaXis Impact mass spectrometer and were obtained from Dr. Lijiang Song, Philip Aston, or James Morrey at the University of Warwick. All mass spectra are reported in units of mass to charge ratio (m/z). Melting points were recorded with a Gallenkamp MDP350 instrument and are reported as observed. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT–IR spectrometer. Optical rotations, $[\alpha]_D^T$, were recorded using an Optical Activity Ltd. AA-1000 millidegree polarimeter and are reported as observed. Analytical thin layer chromatography was performed using Merck 60 F254 pre-coated silica gel plates. Visualisation was achieved by UV light (254 nm). Column chromatography was performed using Apollo Scientific Ltd. 60 40-63 μM silica gel.

All reactions were performed under atmospheric conditions unless otherwise stated.

^{1}H NMR Assignments

CH_x (non-aromatic hydrogen), H_{Ar} (aromatic hydrogen), xH_x (hydrogen attached to heteroatom).

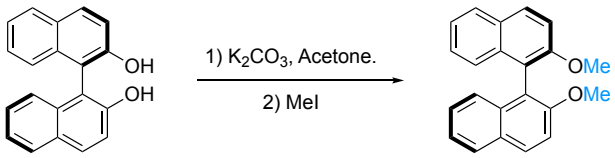
^{13}C NMR Assignments

CH_x (non-aromatic carbon, bonded to hydrogen), C (non-aromatic carbon, not bonded to hydrogens), C_{Ar} (aromatic carbon, not bonded to hydrogen), $C_{Ar}H$ (aromatic carbon, bonded to hydrogen).

6.2 Asymmetric Catalyst Synthesis Procedures

All Brønsted acid catalysts synthesised are known compounds and were generated according to reported procedures, the analytical data obtained from which matched the reported literature data. The methods for the synthesis of the Brønsted acid catalysts protocols are outlined below.

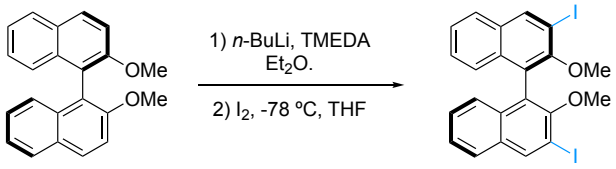
Methylation of BINOL[8]



(*R*)–(+)–2,2'–Dihydroxy–1,1'–dinaphthyl (1 eq.) was added to acetone (4 mL/mmol). The mixture was stirred until homogeneous before anhydrous K_2CO_3 (4 eq.) was added. The heterogeneous mixture was then refluxed under nitrogen atmosphere. Methyl iodide (6 eq.) was then added to the reaction mixture and refluxed for a minimum of 4 h before a second portion of methyl iodide (3 eq.) was added to ensure complete protection. After 18 h the volatile components were removed by rotary evaporation, the resulting residue was then dissolved in distilled water (5 mL/mmol).

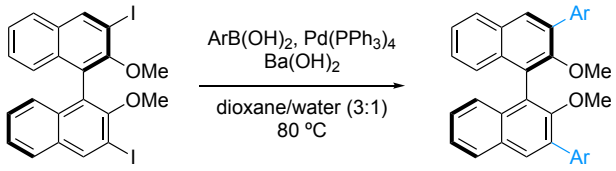
This heterogeneous mixture was stirred for 8 h to ensure maximum K_2CO_3 removal. The resulting white solid was then filtered and dried under vacuum for 12 h to give (*R*)–2,2'–dimethoxy–1,1'–binaphthalene as a white solid (99%).

Iodination of BINOL[6]



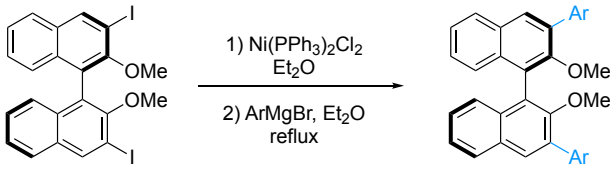
To a vessel under nitrogen was added anhydrous diethyl ether (10 mL/mmol), *n*–butyllithium (3 eq.), and TMEDA (1.4 eq.). The resulting mixture was then stirred at room temperature for 20 mins. (*R*)–2,2'–Dimethoxy–1,1'–binaphthalene (1 eq.) was then added and stirred overnight. The flask was then cooled down to –78 °C before a solution of iodine (2.5 eq.) in anhydrous THF (1.25 mL/mmol) was added drop-wise to the reaction mixture. The reaction mixture was stirred for 1 h at –78 °C and then brought to room temperature. After stirring for 10 h, water (8 mL/mmol) was added slowly, followed by THF (5 mL/mmol). The resulting colourless solution was then stirred for 2 h. The organic layer was then extracted with Et_2O/THF (1:1, 3 x 3 mL/mmol). The combined organics were then washed with Na_2CO_3 (10% aq., 3 x 30 mL) and then water (4 mL/mmol), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. To the resulting crude solution was added Et_2O (4 mL/mmol) and stirred for 1 h to afford (*R*)–3,3'–diiodo–2,2'–dimethoxy–1,1'–binaphthalene as an off–white powder (54%).

Suzuki cross-coupling[6]



To an oven dried two-neck round bottom flask with stirrer bar and condenser was added (*R*)–3,3'–diiodo–2,2'–dimethoxy–1,1'–binaphthalene (1 eq.), the appropriate aryl boronic acid (2.4 eq.), $Pd(PPh_3)_4$ (0.15 eq.), and $Ba(OH)_2$ (5 eq.) were added and the reaction flask put under vacuum and back filled to purge with nitrogen. A mixture of 3:1 dioxane/water (12 mL/mmol) was then added *via* syringe and the reaction brought up to 80 °C for 12 h. Upon completion the reaction mixture was cooled to room temperature and diluted with 1 M AcOH and EtOAc to achieve a biphasic solution. The aqueous layer was then extracted three times with EtOAc and the combined organics washed with H_2O, followed by brine, then drying with $MgSO_4$ and subsequently concentrated under reduced pressure to afford the desired product as a crude mixture.

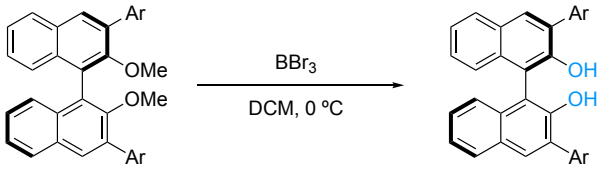
Kumada cross–coupling[8]



An oven-dried, 100-mL, two-necked, round-bottomed flask under nitrogen atmosphere is charged with (*R*)–3,3'–diiodo–2,2'–dimethoxy–1,1'–binaphthalene (1 eq.), and $Ni(PPh_3)_2Cl_2$ (0.1 eq.) in anhydrous Et_2O (12 mL/mmol). To this flask was added freshly prepared Grignard reagent in Et_2O (4 mL/mmol, prepared from appropriate bromide (8 eq.), Mg (16 eq.) in anhydrous Et_2O (6 mL/mmol). The

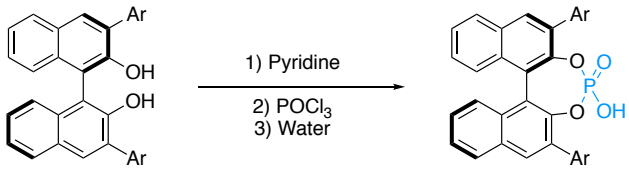
suspension was stirred at room temperature for 10 min and then refluxed for 24 h. The reaction was then cooled to 0 °C and quenched slowly with 1.0 M HCl solution (7 mL/mmol). The two layers were then separated, and the aqueous layer was washed with Et_2O (3 x 7 mL/mmol). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure to afford the desired product as a crude mixture.

Methoxy BINOL deprotection[8]



To a solution of the appropriate crude 3,3'–disubtitued BINOL derivative (1 eq.) in DCM (30 mL/mmol) was slowly added 1.0 M solution of boron tribromide (7 eq.) in DCM (7 mL/mmol) at 0 °C. The reaction mixture was warmed up to room temperature and stirred overnight. The mixture was then cooled to 0 °C and slowly quenched with water (9 mL/mmol). The mixture was then separated, and the aqueous layer was extracted with DCM (3 x 15 mL/mmol). The combined organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure.

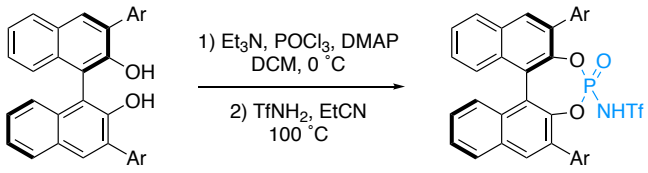
BINOL phosphorylation[6]



A binaphthol derivative (1 eq.) was dissolved in pyridine (2 mL/mmol) under N_2 atmosphere. To the resulting solution was added $POCl_3$ (2 eq.) at RT and the reaction mixture was stirred and monitored by TLC until completion. Water (2 mL/mmol) was added and the resulting suspension was then brought to reflux and monitored to ensure

complete hydrolysis. DCM was then added, and pyridine removed *via* reverse extraction with 1 M HCl. The organic phase was then dried with $MgSO_4$ and concentrated under reduced pressure. The resultant residue was then purified by column chromatography on silica gel to afford the desired product.

BINOL phosphoramidation[7]

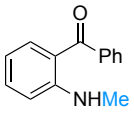


To a solution of the appropriate BINOL derivative (1 eq.) in anhydrous DCM (5 mL/mmol) at 0 °C were added distilled Et_3N (7 eq.), $POCl_3$ (1.2 eq.), and DMAP (2 eq.). The mixture was then brought to room temperature and stirred for 2 h, followed the by addition of EtCN (5 mL/mmol) and then $TfNH_2$ (2 eq.). The reaction was then brought to 100 °C for 24 h. Upon completion the reaction was quenched with water and extracted twice with Et_2O. The combined organics were then washed with sat. aq. $NaHCO_3$ once, and 6 M HCl twice. The resultant organics were then dried over $MgSO_4$ and concentrated under reduced pressure. The obtained crude product was then purified by column chromatography on silica gel (eluent: *n*–hexane–DCM–Et_2O) providing the phosphoramide, potentially as a salt. The product was then washed with 6 M HCl a second time, dried over $MgSO_4$, and concentrated to afford the desired product.

6.3 Experimental Data for Chapter 2

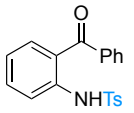
All molecules generated throughout this study are known compounds. The protocols for the synthesis of the model allyl– and propargyl–alcohol substrates, and data for the subsequent rearrangement product, are shown below.

(2–(Methylamino)phenyl)(phenyl)methanone **190a**[1]



Yellow solid (0.18 g, 48%). To a solution of 2–aminobenzophenone (592 mg, 3 mmol) in DMF (7.5 mL) was added K_2CO_3 (0.829 g, 6 mmol) and methyl iodide (0.37 mL, 6 mmol). The reaction was stirred at 80 °C and monitored by TLC analysis until completion and subsequently quenched with water (10 mL). The product was extracted with ethyl acetate (3 x 15 mL) and the combined organics washed with water (3 x 15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to give the title compound. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 8.54 (brs, 1H, J = 8.0 Hz, H_{Ar}), 7.62–7.59 (2H, m, H_{Ar}), 7.54–7.30 (5H, m, H_{Ar}), 6.77 (d, 1H, J = 8.5 Hz, H_{Ar}), 6.57 (t, 1H, J = 7.0 Hz, , H_{Ar}), 3.01 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 199.7, 153.1, 140.4, 134.4, 134.8, 131.0, 129.6, 127.7, 116.9, 113.9, 111.7, 30.1. **MS (ESI): m/z ($C_{14}H_{13}NO$ + Na^+) found:** 234.1.

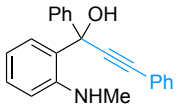
N–(2–Benzoylphenyl)–4–methylbenzenesulfonamide **190b**[2]



White solid (2.33 g, 66%). To a solution of the 2-aminobenzophenone (1.97 g, 10 mmol) in pyridine (5 mL) was added *p*–TsCl (2.3 g, 12 mmol) at room temperature. The resulting solution was stirred for 4 h. On completion, the reaction mixture was quenched with water (5 mL), filtered, and dried. The red/pink solid was then dissolved in DCM and activated charcoal added; hot filtration and subsequent concentration under reduced pressure gave the title compound as a white solid. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 10.05 (s, 1H, NH), 7.85 (d, 1H, J = 8.5 Hz, H_{Ar}), 7.60–7.51 (m, 4H, H_{Ar}), 7.46–7.39 (m, 5H, H_{Ar}), 7.14 (t, 1H, J = 8.5, 7.0 Hz, H_{Ar}), 7.06 (d, 2H J = 8.5 Hz, H_{Ar}), 2.28 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 198.1, 143.2, 138.6,

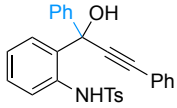
137.9, 135.5, 133.8, 133.1, 132.3, 129.5, 129.1, 128.2, 127.6, 126.7, 123.2, 21.2. **MS (ESI): m/z ($C_{20}H_{17}NO_3S + Na^+$) found:** 374.1.

1–(2–(Methylamino)phenyl)–1,3–diphenylprop–2–yn–1–ol **165a**[1]



To a stirred solution of diisopropylamine (0.21 mL 1.5 mmol) in anhydrous THF at −78 °C was added *n*–butyllithium (2.0 M, 0.75 mL, 1.5 mmol) dropwise, and the resulting solution was stirred for 10 min. Phenylacetylene (0.1 mL, 1 mmol) was added in a dropwise manner. The resulting mixture was stirred for 1 h. In a separate flask, (2–(methylamino)phenyl)(phenyl)methanone (106 mg, 0.5 mmol) was dissolved in THF (2 mL) and added to the LDA mixture dropwise and the resulting solution allowed to stir for 1 h. The reaction mixture was then warmed to room temperature and stirred for 1 h. Upon completion, the reaction mixture was quenched by adding saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting product was then used without further purification.

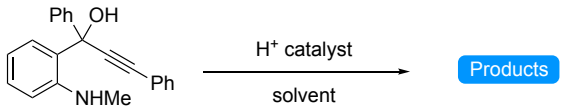
N–(2–(1–hydroxy–1,3–diphenylprop–2–yn–1–yl)phenyl)–4–methylbenzenesulfonamide **165b**[3]



White solid (0.17 g, 76%). To a stirred solution of diisopropylamine (0.21 mL 1.5 mmol) in anhydrous THF at −78 °C was added *n*–butyllithium (2.0 M, 0.75 mL, 1.5 mmol) dropwise, and the resulting solution was stirred for 10 min. Phenylacetylene (0.1 mL, 1 mmol) was added in a dropwise manner. The resulting mixture was stirred for 1 h. In a separate flask, *N*–(2–benzoylphenyl)–4–methylbenzenesulfonamide (175 mg, 0.5 mmol) was dissolved in THF (2 mL) and added to the LDA mixture dropwise and the resulting solution allowed to stir for 1 h. The reaction mixture was then warmed to room temperature and stirred for 1 h. Upon

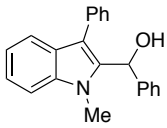
completion, the reaction mixture was quenched by adding saturated NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded the title compound. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 8.81 (brs, 1H, NH), 7.52 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.47 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.36−7.43 (m, 4H, H_{Ar}), 7.33 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.21−7.29 (m, 6H, H_{Ar}), 7.10−7.16 (m, 1H, H_{Ar}), 6.88−6.94 (m, 3H, H_{Ar}), 4.19 (brs, 1H), 2.18 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 143.5, 143.0, 136.6, 131.6, 130.4, 129.9, 129.2, 128.9, 128.6, 128.3, 128.0, 127.6, 127.3, 126.2, 122.3, 121.8, 118.4, 89.8, 89.0, 74.9, 21.2. **MS (ESI): m/z ($C_{28}H_{23}N_3OS$ + Na^+) found:** 476.2.

Optimisation of Propargyl Alcohol Cyclisation



To a small pop-cap vial was added the appropriate solvent (1mL), catalyst (5 mol%) and alcohol substrate **190** (0.5 mmol). The reaction was stirred at the appropriate temperature and monitored by TLC (eluent: 15% EtOAc–*n*–hexane) until completion.

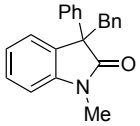
(1–Methyl–3–phenyl–1*H*–indol–2–yl)(phenyl)methanol 168a[1]



Yellow oil. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.68 (d, 1H, J = 8.0 Hz, ArH), 7.51 (d, 2H, J = 7.0Hz, ArH), 7.45 (t, 2H, J = 8.0 Hz, ArH), 7.21–7.36 (m, 8H, ArH), 7.15 (t, 1H, J = 7.5 Hz, ArH), 6.37 (s, 1H, HOC<u>H</u>), 4.21 (brs, 1H, OH), 3.48 (s, 3H, NCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 141.2 (C_{Ar}), 137.9 (C_{Ar}), 135.5 (C_{Ar}), 134.2 (C_{Ar}), 130.0 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.6 ($C_{Ar}H$),

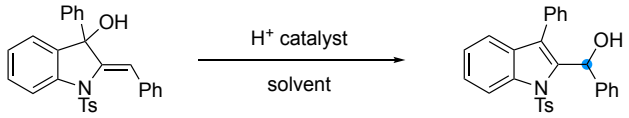
125.7 (C_{Ar}), 122.3 ($C_{Ar}H$), 120.2 ($C_{Ar}H$), 119.7 ($C_{Ar}H$), 117.1 (C_AH), 109.8 ($C_{Ar}H$), 67.7 (CH), 31.8 (CH). **MS (ESI): m/z ($C_{22}H_{19}NO$ + Na^+) found:** 336.1.

3–Benzyl–1–methyl–3–phenylindolin–2–one 188[1]



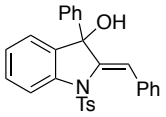
White solid. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.49 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.34 (t, 2H, J = 7.0 Hz, H_{Ar}), 7.28 (d, 1H, J = 7.0 Hz, H_{Ar}), 7.19–7.23 (m, 2H, H_{Ar}), 6.98–7.09 (m, 4H, H_{Ar}), 6.82 (d, 2H, J = 6.5 Hz, H_{Ar}), 6.60 (d, 1H, J = 8.0 Hz, H_{Ar}), 3.69 (d, 1H, J = 13.0 Hz, CH_2), 3.44 (d, 1H, J =13.0 Hz, CH_2), 2.94 (s, 3H, NCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 177.5 (C=O), 143.1 (C_{Ar}), 139.4 (C_{Ar}), 135.4 (C_{Ar}), 131.5 (C_{Ar}), 130.2 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.3 (C_{Ar}), 125.1 ($C_{Ar}H$), 122.5 ($C_{Ar}H$), 108.6 ($C_{Ar}H$), 58.8 (C), 44.6 (CH), 26.9 (CH). **MS (ESI): m/z ($C_{22}H_{19}NO$ + Na^+) found:** 336.1.

Optimisation of the 1,3–Allylic Alcohol Isomerisation of Alcohol 166b



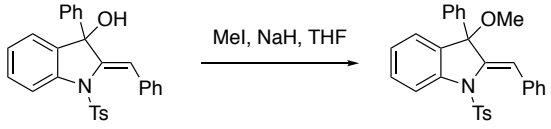
To a small pop-cap vial was added the appropriate solvent (1 mL), catalyst (5 mol%) and alcohol substrate **166b** (0.5 mmol). The reaction was stirred at the appropriate temperature and monitored by TLC (15% EtOAc–*n*–hexane) until completion, or for up to a maximum of five days. The crude reaction mixture was then analysed using NMR. Yields were obtained from the NMR data using CH_2Br_2 as internal standard. Enantiomeric excess was determined using chiral HPLC.

2–Benzylidene–3–phenyl–1–tosylindolin–3–ol **166b**[3]



White solid (224 mg, 99%). To a tinfoil covered round bottomed flask containing a solution of *N*–(2–(1–hydroxy–1,3–diphenylprop–2–yn–1–yl)phenyl)–4–methylbenzenesulfonamide (226 mg, 0.2 mmol) in MeCN (2 mL) was added AgOAc (0.01 mmol). The reaction was stirred at room temperature and monitored by TLC analysis. Upon completion, the reaction mixture was filtered through Celite, washed with DCM (10 mL), and concentrated under reduced pressure. Purification by column chromatography on silica gel afford the title compound. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 7.93 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.67 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.43-7.46 (m, 1H, H_{Ar}), 7.38 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.34 (t, 2H, J = 7.5 Hz, H_{Ar}), 7.17-7.24 (m, 7H, H_{Ar}), 7.06 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.99 (d, 1H, J = 7.0 Hz, H_{Ar}), 6.26 (s, 1H, CH), 2.33 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 145.4 (C_{Ar}), 145.0 (C_{Ar}), 142.6 (C), 142.0 (C_{Ar}), 138.4 (C_{Ar}), 135.7 (C_{Ar}), 133.1 ($C_{Ar}H$), 130.1 ($C_{Ar}H$), 129.7 ($C_{Ar}H$), 129.5 (C_{Ar}), 128.5 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 125.5 ($C_{Ar}H$), 125.1 ($C_{Ar}H$), 119.7 (CH), 81.9 (C), 21.7 (CH). **MS (ESI): m/z ($C_{28}H_{23}NO_3S$ - H^+) found:** 452.1.

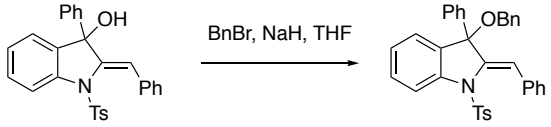
2–Benzylidene–3–methoxy–3–phenyl–1–tosylindoline **166b–Me**



To a stirred solution of 2-benzylidene-3-phenyl-1-tosylindolin-3-ol (0.5 mmol) in anhydrous THF (5 mL) at 0 °C was added portion–wise NaH (0.55 mmol). MeI (0.55 mmol) was then added dropwise over 10 min and brought up to room temperature, allowed to stir for 1 h, and subsequently quenched with water. The product was

extracted with ethyl acetate (3 x 15 mL) and the combined organics washed with water (3 x 15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to give the title compound. White solid (166 mg, 71% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 7.91 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.68 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.45-7.47 (m, 1H, H_{Ar}), 7.39 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.32 (t, 2H, J = 7.5 Hz, H_{Ar}), 7.19-7.25 (m, 7H, H_{Ar}), 7.01 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.94 (d, 1H, J = 7.0 Hz, H_{Ar}), 5.87 (s, 1H, =CH), 3.45 (s, 3H, CH), 2.28 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 145.6 (C_{Ar}), 144.7 (C_{Ar}), 140.3 (C), 142.5 (C_{Ar}), 139.0 (C_{Ar}), 135.5 (C_{Ar}), 133.3 ($C_{Ar}H$), 130.0 ($C_{Ar}H$), 129.8 ($C_{Ar}H$), 129.2 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 125.3 ($C_{Ar}H$), 123.1 (CH), 92.3 (C), 55.6 (CH), 21.9 (CH). **IR (neat, ν_{max}, cm^{-1}):** 2965, 2858, 1729, 1604, 1388, 1160, 1067, 801. **MS (ESI) m/z calcd. ($C_{29}H_{25}NO_3S + Na^+$):** 490.1453, **found:** 490.1469 ($M + Na^+$).

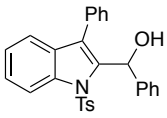
2–Benzylidene–3–ethoxy–3–phenyl–1–tosylindoline 166b–Bn



To a stirred solution of 2-benzylidene-3-phenyl-1-tosylindolin-3-ol (0.5 mmol) in anhydrous THF (5 mL) at 0 °C was added portion–wise NaH (0.55 mmol). BnBr (0.55 mmol) was then added dropwise over 10 min and brought up to room temperature, allowed to stir for 1 h, and subsequently quenched with water. The product was extracted with ethyl acetate (3 x 15 mL) and the combined organics washed with water (3 x 15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel to

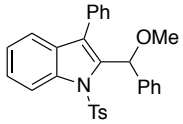
give the title compound. White solid (220 mg, 81% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 7.93 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.74 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.46-7.49 (m, 1H, H_{Ar}), 7.43 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.29–7.37 (m, 7H, H_{Ar}), 7.14-7.27 (m, 7H, H_{Ar}), 7.08 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.87 (d, 1H, J = 7.0 Hz, H_{Ar}), 5.39 (s, 1H, C=CH), 4.87 (s, 2H, OCH_2), 2.35 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 145.5 (C_{Ar}), 144.8 (C_{Ar}), 140.1 (C), 142.7 (C_{Ar}), 139.5 (C_{Ar}), 136.2 (C_{Ar}), 135.7 (C_{Ar}), 133.2 ($C_{Ar}H$), 130.8 ($C_{Ar}H$), 129.9 ($C_{Ar}H$), 129.5 (C_{Ar}), 129.0 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 126.1 ($C_{Ar}H$), 125.1 ($C_{Ar}H$), 123.0 (CH), 110.9 (C), 75.3 (CH), 22.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 2894, 1591, 1372, 1124, 1038, 832. **MS (ESI) m/z calcd. ($C_{35}H_{29}NO_3S$ + Na^+):** 566.1766, **found:** 566.1751 (M + Na^+).

2–Benzylidene–3–phenyl–1–tosylindolin–3–ol **168b**[3]



Yellow oil. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.08 (d, 1H, J = 8.5 Hz, H_{Ar}), 7.51 (d, 2H, J = 7.0 Hz, H_{Ar}), 7.47 (t, 3H, J = 8.0 Hz, H_{Ar}), 7.36-7.42 (m, 4H, H_{Ar}), 7.25−7.30 (m, 7H, H_{Ar}), 7.09 (d, 2H, J = 8.0 Hz, H_{Ar}), 6.34 (d, 1H, J = 12.0 Hz, CH), 4.75 (d, 1H, J = 12.0 Hz, OH), 2.35 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 144.1 (C_{Ar}), 143.7 (C_{Ar}), 136.3 (C_{Ar}), 135.5 (C_{Ar}), 134.4 (C_{Ar}), 131.4 (C_{Ar}), 129.1 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 124.8 ($C_{Ar}H$), 124.7 ($C_{Ar}H$), 124.0 ($C_{Ar}H$), 119.6 ($C_{Ar}H$), 113.8 (C_{Ar}), 67.7 (CH), 20.7 (CH). **MS (ESI): m/z ($C_{28}H_{23}NO_3S$ - H^+) found:** 452.1.

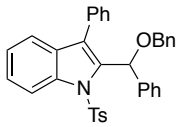
2–(Methoxy(phenyl)methyl)–3–phenyl–1–tosyl–1*H*–indole **168b–Me**



Yellow oil (5.5 mg, 12% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 8.11 (d, 1H, J = 8.5 Hz, H_{Ar}), 7.53 (d, 2H, J = 7.0 Hz, H_{Ar}), 7.49 (t,

3H, *J* = 8.0 Hz, H_{Ar}), 7.37-7.44 (m, 4H, H_{Ar}), 7.22−7.29 (m, 7H, H_{Ar}), 7.12 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 5.94 (s, 1H, =CH), 3.50 (s, 3H, CH), 2.33 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 144.6 (C_{Ar}), 144.1 (C_{Ar}), 136.8 (C_{Ar}), 135.4 (C_{Ar}), 134.9 (C_{Ar}), 132.1 (C_{Ar}), 129.5 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 125.5 ($C_{Ar}H$), 124.9 ($C_{Ar}H$), 124.5 ($C_{Ar}H$), 119.8 ($C_{Ar}H$), 114.3 (C_{Ar}), 78.1 (CH), 69.8 (CH), 21.2 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3072, 2525, 1390, 1154, 956. **MS (ESI) m/z calcd. ($C_{29}H_{25}NO_3S$ + Na^+):** 490.1453, **found:** 490.1469 (M + Na^+).

2–((Benzyloxy)(phenyl)methyl)–3–phenyl–1–tosyl–1*H*–indole **168b–Bn**

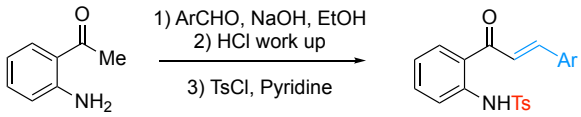


Colourless oil (35.5 mg, 65% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 8.05 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 7.59 (d, 2H, *J* = 7.0 Hz, H_{Ar}), 7.45 (t, 3H, *J* = 8.0 Hz, H_{Ar}), 7.35-7.41 (m, 5H, H_{Ar}), 7.31–7.35 (m, 4H, H_{Ar}), 7.22−7.31 (m, 7H, H_{Ar}), 7.02 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 5.91 (s, 1H, CH), 4.52 (s, 2H, OCH_2), 2.37 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 143.9 (C_{Ar}), 143.6 (C_{Ar}), 138.8 (C_{Ar}), 136.5 (C_{Ar}), 135.7 (C_{Ar}), 135.2 (C_{Ar}), 134.8 (C_{Ar}), 132.1 (C_{Ar}), 129.6 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 125.9 ($C_{Ar}H$), 125.0 ($C_{Ar}H$), 124.4 ($C_{Ar}H$), 124.2 ($C_{Ar}H$), 119.8 ($C_{Ar}H$), 115.2 (C_{Ar}), 78.5 (CH), 72.1 (CH), 21.1 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3020, 2499, 1367, 1117, 921. **MS (ESI) m/z calcd. ($C_{35}H_{29}NO_3S$ + Na^+):** 566.1766, **found:** 566.1751 (M + Na^+).

6.4 Experimental Data for Chapter 3

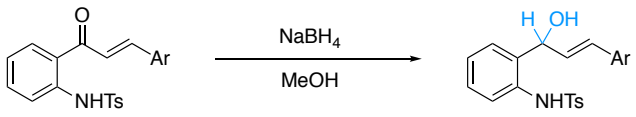
6.4.1 General Procedures[4]

Construction of the *N*–tosyl α,β–unsaturated ketone scaffold **226**



To an EtOH (10 mL/mmol) solution containing the 2'–aminoacetophenone (1 mmol), aldehyde (1 eq.), at room temperature was added 2.5 M NaOH (0.6 mL/mmol) and the resulting reaction mixture was allowed to stir for 4 h. On completion, the reaction mixture was quenched by the addition of 1 M HCl (10 mL/mmol) and the solvent was removed under reduced pressure. The crude 2'–aminochalcone was taken up in pyridine (0.4 mL/mmol) and *p*–TsCl (1.6 eq.) was added in one portion at room temperature under a nitrogen atmosphere. The resulting reaction mixture was then stirred at room temperature for 4 h. After which, the solvent was removed under reduced pressure and the crude mixture was purified by column chromatography on silica gel with DCM as eluent. At this stage, one of two methods were employed:

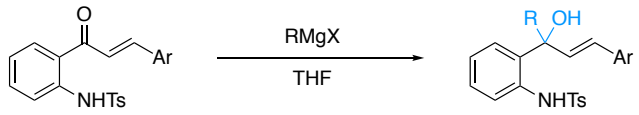
Procedure 1: Sodium borohydride reduction to **169**



The *N*–tosyl 2'–aminochalcone (3.0 mmol) was dissolved in methanol (30 mL/mmol) and cooled to 0 °C. Sodium borohydride (1.3 eq.) was added in one portion and the reaction mixture was allowed to stir for 3 h. Upon completion, the reaction mixture was quenched by the addition of water (1 mL/mmol) and the solvent was removed under reduced pressure. The crude mixture was dissolved in DCM (10 mL/mmol), washed with water (10 mL), brine (10 mL), dried over magnesium sulphate, and

concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (eluent: 2:1 PhMe–DCM) to afford the secondary alcohol substrate.

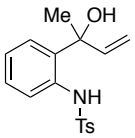
Procedure 2: Grignard addition to **169**



The tosyl–protected 2'–aminochalcone (3.0 mmol) was dissolved in THF (60 mL/mmol) and a solution of alkyl or aryl magnesium bromide (1 M in THF solution, 4.5 mmol) was added at 0 °C and subsequently allowed to slowly return to room temperature. The reaction mixture was allowed to stir at room temperature for 24 h and the progress of the reaction was followed by TLC analysis and mass spectrometry. Upon completion, the reaction mixture was quenched with saturated NH_4Cl (60 mL/mmol). After additional stirring at room temperature for 10 min, EtOAc (90 mL/mmol) was added and the organic phase was separated. The aqueous phase was further extracted with EtOAc (3 x 30 mL/mmol) and the combined organic layers were washed with brine (60 mL), dried over anhydrous magnesium sulphate and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (eluent: 2:1 PhMe–DCM) to afford the tertiary alcohol substrate.

6.4.2 Compound Data

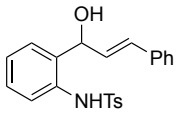
N-(2-(2-Hydroxybut-3-en-2-yl)phenyl)-4-methylbenzenesulfonamide **169a**[4a]



White solid (0.85 g, 90% yield); T_m = 140–144 °C. Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 500 MHz):** δ 9.95 (s, 1H, NH), 7.74 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.59 (dd, 1H, *J* = 8.0, 1.0 Hz,

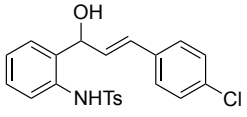
H_{Ar}), 7.31 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.19 (ddd, 2H, *J* = 15.5, 7.5, 1.5 Hz, H_{Ar}), 6.96 (td, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 5.94 (dd, 1H, *J* = 17.0, 10.5 Hz, CH), 5.17 (dd, 1H, *J* = 17.5, 1.0 Hz, CH), 5.00 (dd, 1H, *J* = 10.5, 1.0 Hz, CH), 2.35 (s, 3H, CH_3), 1.61 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 143.4 (CH), 143.3 (C_{Ar}), 137.3 (C_{Ar}), 136.8 (C_{Ar}), 132.7 (C_{Ar}), 129.2 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 122.6 ($C_{Ar}H$), 118.4 ($C_{Ar}H$), 111.9 (CH), 76.0 (C), 27.9 (CH), 20.3 (CH). **MS (ESI): m/z ($C_{17}H_{19}NO_3S$ - H^+) found:** 316.1.

N-(2-(1-Hydroxy-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide **169b**[4a]



White solid (1.02 g, 90% yield); T_m = 84–86 °C. Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 400 MHz):** δ 7.70–7.63 (m, 2H, H_{Ar}), 7.52 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.40–7.31 (m, 4H, H_{Ar}), 7.21 (td, 6H, *J* = 12.0, 8.0 Hz, H_{Ar}), 7.06 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 6.59 (dd, 1H, *J* = 16.0, 2.0 Hz, CH), 6.20 (dd, 1H, *J* = 16.0, 5.5 Hz, CH), 5.47 (d, 1H, *J* = 5.5 Hz, CH), 2.29 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 100 MHz):** δ 143.5 (C_{Ar}), 137.3 (C_{Ar}), 136.7 (C_{Ar}), 136.2 (C_{Ar}), 132.8 (C_{Ar}), 130.5 (CH), 129.7 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.5 (CH), 124.2 ($C_{Ar}H$), 120.7 ($C_{Ar}H$), 73.7 (CH), 20.5 (CH). **MS (ESI): m/z ($C_{22}H_{20}NO_3S$ - H^+) found:** 378.1.

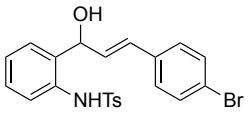
N-(2-(3-(4-Chlorophenyl)-1-hydroxyallyl)phenyl)-4-methylbenzenesulfonamide **169c**[4a]



Colourless oil (1.04 g, 84% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 500 MHz):** δ 7.69–7.65 (m, 2H, H_{Ar}), 7.51 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.38 (s, 4H, H_{Ar}), 7.28–7.19 (m, 4H, H_{Ar}), 7.09 (dd, 1H, *J* = 8.0, 7.0 Hz, H_{Ar}), 6.60 (dd, 1H, *J* = 16.0, 2.0 Hz, CH), 6.25 (dd, 1H, *J* = 16.0, 5.5 Hz, CH), 5.51 (dd, 1H, *J* = 5.5, 1.5 Hz, CH), 2.32

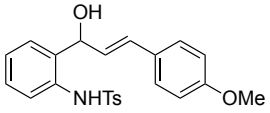
(s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 143.6 (C_{Ar}), 137.4 (C_{Ar}), 136.1 (C_{Ar}), 135.6 (C_{Ar}), 132.9 (C_{Ar}), 132.7 (C_{Ar}), 131.6 ($C_{Ar}H$), 129.5 (CH), 128.6 (CH), 128.4 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 124.4 ($C_{Ar}H$), 121.1 ($C_{Ar}H$), 73.4 (CH), 20.5 (CH_3). **MS (ESI): m/z ($C_{22}H_{19}NClO_3S$ - H^+) found:** 412.1 and 414.1.

N-(2-(3-(4-Bromophenyl)-1-hydroxyallyl)phenyl)-4-methylbenzenesulfonamide **169d** [4a]



Colourless oil (1.12 g, 82% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 500 MHz):** δ 7.69–7.62 (m, 2H, H_{Ar}), 7.55–7.48 (m, 3H, H_{Ar}), 7.34–7.28 (m, 3H, H_{Ar}), 7.28–7.15 (m, 5H, H_{Ar}), 7.07 (td, 1H, *J* = 7.5, 1.0 Hz, H_{Ar}), 6.57 (dd, 1H, *J* = 16.0, 1.5 Hz, CH), 6.25 (dd, 1H, *J* = 16.0 and 5.5 Hz, CH), 5.49 (dd, 1H, *J* = 5.5 and 1.5 Hz, CH), 2.30 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 143.6 (C_{Ar}), 137.4 (C_{Ar}), 136.1 (C_{Ar}), 136.0 (C_{Ar}), 132.9 (C_{Ar}), 131.7 ($C_{Ar}H$), 131.6 ($C_{Ar}H$), 129.5 (CH), 128.5 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.2 (CH), 124.4 ($C_{Ar}H$), 121.1 ($C_{Ar}H$), 120.8 (C_{Ar}), 73.4 (CH), 20.6 (CH_3). **MS (ESI): m/z ($C_{22}H_{19}NBrO_3S$ - H^+) found:** 456.0 and 458.0.

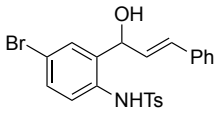
N-(2-(1-Hydroxy-3-(4-methoxyphenyl)allyl)phenyl)-4-methylbenzenesulfonamide **169e** [4b]



Yellow oil (1.04 g, 85% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 500 MHz):** δ 8.39 (d, 1H, *J* = 5.5 Hz, H_{Ar}), 7.67–7.61 (m, 2H, H_{Ar}), 7.26–7.05 (m, 12H, H_{Ar}), 6.87–6.80 (m, 3H, H_{Ar}), 6.44 (dd, 1H, *J* = 16.0, 1.5 Hz, CH), 6.04 (dd, 1H, *J* = 16.0 and 6.5 Hz CH), 5.25 (d, 1H, *J* = 6.0 Hz, CH), 3.80 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 131.2 (C_{Ar}), 129.6 (C_{Ar}), 129.6 (C_{Ar}), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 129.1 (CH), 128.9 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.6 (CH), 125.3

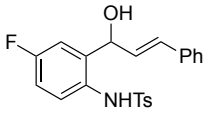
($C_{Ar}H$), 124.5 ($C_{Ar}H$), 121.6 ($C_{Ar}H$), 114.0 ($C_{Ar}H$), 113.9 ($C_{Ar}H$), 113.8 ($C_{Ar}H$), 74.9 (CH), 55.3 (CH), 21.6 (CH). **MS (ESI): m/z ($C_{23}H_{24}NO_4S$ - H^+) found:** 408.1.

N-(4-Bromo-2-(1-hydroxy-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide **169e**



Yellow oil (1.03 g, 88% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 9.07 (brs, 1H, NH), 7.62 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.43 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 7.28–7.37 (m 7H, H_{Ar}), 7.08 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.53 (d, 1H, *J* = 16.0 Hz, CH), 6.11 (dd, 1H, *J* = 16.0, 6.0 Hz, CH), 5.62 (brs, 1H, OH) 5.24 (d, 1H, *J* = 5.5 Hz, CH), 2.32 (3H, s). **^{13}C NMR (d6-acetone, 125 MHz):** δ 162.5 (C_{Ar}), 144.1 (C_{Ar}), 135.9 (C_{Ar}), 135.2 (C_{Ar}), 133.6 (C_{Ar}), 132.3 ($C_{Ar}H$), 131.9 ($C_{Ar}H$), 131.3 ($C_{Ar}H$), 129.8 (CH), 128.8 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.9 (CH), 123.4 ($C_{Ar}H$), 117.7 (C_{Ar}), 74.3 (CH), 21.7 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3471, 3232, 2925, 2855, 1597, 1487, 1384, 1330, 1161, 1091, 905, 729, 650. **MS (ESI) m/z calcd. ($C_{22}H_{20}BrNO_3S$ + Na^+):** 480.0239 & 482.0221, **found:** 480.0240 & 482.0222 (M + Na^+).

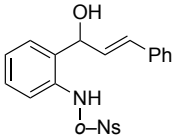
N-(4-Fluoro-2-(1-hydroxy-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide **169g**



Pale yellow oil (0.86 g, 72% yield). **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 7.78 (s, 1H, NH), 7.61 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.39–7.42 (m, 1H, H_{Ar}), 7.28–7.37 (m, 5H, H_{Ar}), 7.15 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.93 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.54 (d, 1H, *J* = 16.0 Hz, CH), 6.13 (dd, 1H, *J* = 16.0, 6.5 Hz, CH), 5.16–5.28 (m, 1H, CH), 2.41 (d, 1H, *J* = 3.5 Hz), 2.36 (s, 3H). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 160.2 (d, *J* = 246 Hz, $C_{Ar}F$), 144.0 (C_{Ar}), 136.7 (C_{Ar}), 135.9 (C_{Ar}), 135.8 (d, J = 7 Hz, C_{Ar}), 132.5 (CH), 131.4 (d, *J* = 3.0 Hz, C_{Ar}), 129.8 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.9 (CH), 125.5 (d, J = 8.0 Hz, $C_{Ar}H$), 115.7 (d, *J* = 23.0 Hz, $C_{Ar}H$), 115.2 (d, *J* = 24.0 Hz, $C_{Ar}H$), 73.5 (CH), 21.7 (CH). **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –116.0. **IR (neat, ν_{max}, cm^{-1}):** 3471, 3266, 2960, 2924, 2853, 1597, 1496,

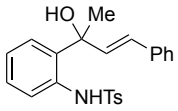
1393, 1330, 1159, 1091, 908, 796, 693, 664, 549. **MS (ESI) m/z calcd. ($C_{22}H_{20}FNO_3S$ + Na^+):** 420.1040, **found:** 420.1036 (M + Na^+).

N-(2-(1-Hydroxy-3-phenylallyl)phenyl)-2-nitrobenzenesulfonamide 169h



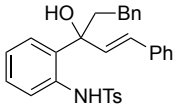
Light orange oil (0.65 g, 53% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 9.62 (brs, 1H, NH), 7.93–7.95 (m, 1H, H_{Ar}), 7.73–7.75 (m, 1H, H_{Ar}), 7.58–7.67 (m, 4H, H_{Ar}), 7.47–7.52 (m, 2H, H_{Ar}), 7.28–7.31 (m, 5H, H_{Ar}), 7.18 (d, 1H, *J* = 7.5 Hz, H_{Ar}), 6.48 (d, 1H, *J* = 16.0 Hz, CH), 6.35 (dd, 1H, *J* = 16.0, 6.0 Hz, CH), 5.62 (s, 1H, OH), 5.56 (d, 1H, *J* = 6.0 Hz. CH). **^{13}C NMR (d6-acetone, 125 MHz):** δ 136.1 (C_{Ar}), 134.8 (C_{Ar}), 134.5 (C_{Ar}), 133.8 (C_{Ar}), 132.7 ($C_{Ar}H$), 131.8 (C_{Ar}), 131.2 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 129.1 (CH), 129.1 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 126.8 (CH), 126.3 ($C_{Ar}H$), 125.4 ($C_{Ar}H$), 123.8 ($C_{Ar}H$), 73.3 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3482, 3217, 2926, 1693, 1586, 1538, 1493, 1303, 1163, 1124, 966, 853, 752, 732, 693, 584, 559. **MS (ESI) m/z calcd. ($C_{21}H_{18}N_2O_5S$ + Na^+):** 433.0834, **found:** 433.0831 (M + Na^+).

N-(2-(2-Hydroxy-4-phenylbut-3-en-2-yl)phenyl)-4-methylbenzenesulfonamide 169i [4b]



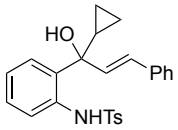
Pale yellow oil (0.89 g, 76% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 500 MHz):** δ 10.03 (s, 1H, NH), 7.64 (t, 3H, *J* = 9.0 Hz, H_{Ar}), 7.40–7.32 (m, 4H, H_{Ar}), 7.28 (dd, 2H, *J* = 7.5, 1.5 Hz, H_{Ar}), 7.20 (td, 1H, *J* = 8.0, 1.5 Hz, H_{Ar}), 7.05 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.98 (td, 1H, *J* = 7.51, 1.5 Hz, H_{Ar}), 6.61 (d, 1H, *J* = 16.0 Hz, CH), 6.36 (d, 1H, *J* = 16.0 Hz, CH), 5.77 (s, 1H, OH), 2.24 (s, 3H, CH_3), 1.75 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 143.3 (C_{Ar}), 137.1 (C_{Ar}), 136.9 (C_{Ar}), 136.7 (C_{Ar}), 135.0 ($C_{Ar}H$), 133.0 (C_{Ar}), 129.2 (CH), 128.5 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.5 (CH), 122.8 ($C_{Ar}H$), 118.3 ($C_{Ar}H$), 76.0 (C), 28.6 (CH), 20.4 (CH). **MS (ESI): m/z ($C_{23}H_{23}NO_3S$ + H^+) found:** 394.1.

N-(2-(3-Hydroxy-1,5-diphenylpent-1-en-3-yl)phenyl)-4-methylbenzenesulfonamide 169j



Colourless oil (0.74 g, 51% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 11.41 (s, 1H, NH), 8.02 (dd, 1H, *J* = 8.0, 1.5 Hz, H_{Ar}), 7.66 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 7.60 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.55–7.49 (m, 1H, H_{Ar}), 7.32 (d, 4H, *J* = 4.4 Hz), 7.29–7.18 (m, 6H, H_{Ar}), 7.18–7.08 (m, 4H, H_{Ar}), 3.41 (d, 2H, *J* = 6.0 Hz, CH), 3.33 (td, 1H, *J* = 8.5, 7.5, 3.5 Hz, CH), 2.48 (td, 2H, *J* = 9.5, 6.0 Hz, CH), 2.28 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 144.4 (C_{Ar}), 144.0 (C_{Ar}), 142.1 (C_{Ar}), 139.7 (C_{Ar}), 136.5 (C_{Ar}), 134.6 ($C_{Ar}H$), 131.7 ($C_{Ar}H$), 129.7 (CH), 128.4 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.1 (CH), 126.3 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 122.9 ($C_{Ar}H$), 122.7 (C_{Ar}), 118.9 ($C_{Ar}H$), 46.2 (C), 38.0 (CH_2), 33.4 (CH_2), 20.4 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3479, 3171, 3061, 3027, 2926, 1651, 1601, 1578, 1494, 1452, 1334, 1159, 1119, 752, 700, 565. **MS (ESI) m/z calcd. ($C_{30}H_{29}NO_3S$ + Na^+):** 506.1760, **found:** 506.1763 ($M + Na^+$).

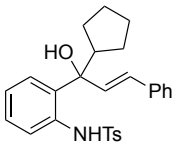
N-(2-(1-Cyclopropyl-1-hydroxy-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide 169k



Off-white oil (0.80 g, 63% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 9.18 (s, 1H, NH), 7.63 (dd, 2H, *J* = 9.5, 8.0 Hz, H_{Ar}), 7.55 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.30–7.34 (m, 3H, H_{Ar}), 7.14–7.24 (m, 3H, H_{Ar}), 7.02 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 6.82 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 6.51 (d, 1H, *J* = 16.0 Hz, CH), 5.83 (d, 1H, *J* = 16.0 Hz, CH), 5.52 (s, 1H, OH), 2.19 (s, 3H, CH_3), 1.52–1.57 (m, 1H, CH), 0.69–0.73 (m, 1H, CH), 0.59–0.63 (m, 1H, CH), 0.47-0.54 (m, 2H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** δ 143.3 (C_{Ar}), 136.8 (C_{Ar}), 136.2 (C_{Ar}), 132.0 (C_{Ar}), 130.5 (C_{Ar}), 129.8 ($C_{Ar}H$), 129.4 (CH), 128.8 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.9 (CH), 123.2 ($C_{Ar}H$), 119.2 ($C_{Ar}H$), 78.9 (C), 22.4 (CH), 21.6 (CH), 3.9 (CH_2), 0.2 (CH_2). **IR (neat, ν_{max}, cm^{-1}):** 3456, 3217, 3081, 3026, 2923, 2854, 1599,

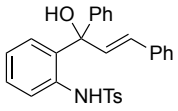
1583, 1558, 1494, 1449, 1402, 1334, 1159, 1091, 975, 929, 751, 661, 566, 545. **MS (ESI) m/z calcd. ($C_{25}H_{25}NO_3S + Na^+$):** 442.1447, **found:** 442.1446 ($M + Na^+$).

N-(2-(1-Cyclopentyl-1-hydroxy-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide 169l



Yellow oil (0.92 g, 69% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 11.41 (s, 1H, NH), 8.03 (dd, 1H, *J* = 8.0, 1.5 Hz, H_{Ar}), 7.63 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 7.58 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.52–7.46 (m, 1H, H_{Ar}), 7.25 (dd, 6H, *J* = 6.0, 3.0 Hz, H_{Ar}), 7.16 (dq, 1H, *J* = 6.0, 3.0 Hz, H_{Ar}), 7.13–7.07 (m, 1H, H_{Ar}), 3.53 (dd, 1H, *J* = 17.0, 9.5 Hz, CH), 3.39 (dd, 1H, *J* = 17.0, 4.0 Hz), 3.09 (td, 1H, *J* = 10.0, 4.0 Hz, CH), 2.32 (s, 3H, CH_3), 2.16-2.32 (m, 1H, CH), 1.91-1.92 (m, 1H, CH), 1.65-1.67 (m, 1H, CH), 1.55-1.58 (m ,2H, CH), 1.44-1.53 (m, 1H, CH), 1.25-1.31 (m, 2H, CH), 1.04-1.08 (m, 1H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** δ 144.8 (C_{Ar}), 144.0 (C_{Ar}), 139.7 (C_{Ar}), 136.5 (C_{Ar}), 131.8 ($C_{Ar}H$), 129.7 (CH), 128.1 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.1 (CH), 126.0 ($C_{Ar}H$), 122.8 ($C_{Ar}H$), 122.7 (C_{Ar}), 118.7 ($C_{Ar}H$), 46.2 (CH), 45.2 (C), 31.3 (CH_2), 31.2 (CH_2), 25.0 (CH_2), 24.6 (CH_2), 20.5 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3438, 2952, 1700, 1649, 1493, 1451, 1335, 1246, 1159, 1090, 916, 813, 756, 701, 657, 628, 562, 544. **MS (ESI) m/z calcd. ($C_{27}H_{28}NO_3S - H^+$):** 446.1795, **found:** 446.1791 ($M - H^+$).

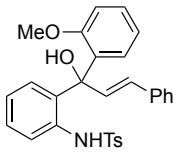
N-(2-(1-Hydroxy-1,3-diphenylallyl)phenyl)-4-methylbenzenesulfonamide 169m



Colourless oil (0.87 g, 64% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 8.97 (s, 1H, NH), 7.62 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.18–7.34 (m, 14H, H_{Ar}), 7.07 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 6.94 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.63 (d, 1H, *J* = 16.0 Hz, CH), 6.24 (d, 1H, *J* = 16.0 Hz, CH), 3.00 (s, 1H, OH), 2.27 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.8 (C_{Ar}), 143.3 (C_{Ar}), 136.8 (C_{Ar}), 136.4 (C_{Ar}), 136.1 (C_{Ar}), 133.8 ($C_{Ar}H$), 132.3 ($C_{Ar}H$), 130.9 ($C_{Ar}H$), 129.5 (CH), 129.3 ($C_{Ar}H$), 129.1 ($C_{Ar}H$),

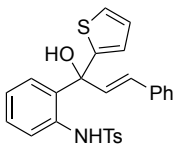
128.8 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.8 (CH), 122.7 ($C_{Ar}H$), 119.2 ($C_{Ar}H$), 81.3 (C), 21.6 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3444, 3207, 3060, 3027, 2923, 1600, 1583, 1493, 1449, 1402, 1331, 1282, 1156, 1091, 976, 941, 907, 752, 733, 700, 662, 565, 545. **MS (ESI) m/z calcd. ($C_{28}H_{25}NO_3S$ + Na^+):** 478.1447, **found:** 478.1445 (M + Na^+).

N-(2-(1-Hydroxy-1-(2-methoxyphenyl)-3-phenylallyl)phenyl)-4-methylbenzenesulfonamide 169n



Colourless oil (0.97 g, 66% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 9.73 (brs, 1H, NH), 7.71 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.57 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.28–7.41 (m, 5H, H_{Ar}), 7.19 (t, 1H, *J* = 8.0 Hz, H_{Ar}), 6.79–7.04 (m, 7H, H_{Ar}), 6.69 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 6.52 (d, 1H, *J* = 16.0 Hz, CH), 6.18 (d, 1H, *J* = 16.0 Hz, CH), 5.67 (s, 1H, OH), 3.74 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 157.1 (C_{Ar}), 143.2 (C_{Ar}), 137.3 (C_{Ar}), 136.9 (C_{Ar}), 136.4 (C_{Ar}), 132.4 ($C_{Ar}H$), 131.9 (C_{Ar}), 131.5 (C_{Ar}), 130.9 ($C_{Ar}H$), 129.8 ($C_{Ar}H$), 129.4 (CH), 128.9 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.1 (CH), 122.4 ($C_{Ar}H$), 121.3 ($C_{Ar}H$), 118.5 ($C_{Ar}H$), 112.4 ($C_{Ar}H$), 81.9 (C), 56.0 (CH_3), 21.6 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3473, 3212, 3028, 2926, 2856, 1599, 1583, 1490, 1455, 1401, 1336, 1284, 1236, 1159, 1092, 910, 753, 661, 565, 545. **MS (ESI) m/z calcd. ($C_{29}H_{27}NO_4S$ + Na^+):** 508.1553, **found:** 508.1553 (M + Na^+).

N-(2-(1-Hydroxy-3-phenyl-1-(thiophen-2-yl)allyl)phenyl)-4-methylbenzenesulfonamide 169o



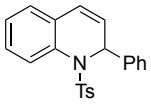
Pale yellow oil (1.05 g, 76% yield). **^{1}H NMR (d6-acetone, 500 MHz):** δ 9.22 (brs, 1H, NH), 7.67 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.49 (d, 2H, *J* = 8.0 Hz, H_{HetAr}), 7.31–7.33 (m, 6H), 7.14–7.23 (m, 2H), 7.04 (d, 1H, *J* = 8.0 Hz, H_{HetAr}), 6.93–6.96 (m, 4H, H_{Ar}), 6.79 (d, 1H, *J* = 7.5 Hz, H_{Ar}), 6.62 (d, 1H,

J = 16.0 Hz, CH), 6.33 (d, 1H, *J* = 16.0 Hz, CH), 2.26 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** δ 149.1 (C_{HetAr}), 143.4 (C_{Ar}), 136.7 (C_{Ar}), 136.6 (C_{Ar}), 135.9 (C_{Ar}), 132.9 ($C_{Ar}H$), 131.7 (C_{Ar}), 131.2 ($C_{Ar}H$), 129.5 (CH), 129.3 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 127.0 (CH), 126.5 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 122.9 ($C_{Ar}H$), 119.3 ($C_{Ar}H$), 79.9 (C), 21.60 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3426, 3238, 3064, 3029, 2924, 1650, 1600, 1583, 1494, 1452, 1403, 1333, 1158, 1091, 972, 911, 828, 752, 704, 566, 545. **MS (ESI) m/z calcd. ($C_{26}H_{22}NO_3S_2$ - H$^+$):** 460.1047, **found:** 460.1040 (M – H$^+$).

General procedure for the TfOH-catalysed allylic amination[5]

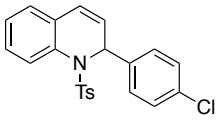
To a round-bottom flask containing the allylic alcohol substrate (0.2 mmol) open to the air was added 2 mL of TfOH (0.01 mol %) from a stock solution. Reaction progress was monitored to completion by TLC analysis. The crude mixture was quenched with water (2 mL/0.2 mmol of substrate), extracted with EtOAc (3 x 10 mL), and concentrated under reduced pressure. Purification by column chromatography on silica gel (eluent: 100% toluene, or 10:1 *n*–hexane–EtOAc) furnished the title compound.

2-Phenyl-1-tosyl-1,2-dihydroquinoline 171b[4a]



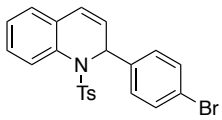
Colourless oil (54 mg, 75% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR (d6-acetone, 400 MHz):** δ 7.63 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.33-7.41 (m, 4H, H_{Ar}), 7.33–7.22 (m, 6H, H_{Ar}), 7.19 (d, 1H, *J* = 7.5 Hz, H_{Ar}), 7.09 (d, 1H, *J* = 7.5 Hz, H_{Ar}), 6.40 (d, 1H, *J* = 9.5 Hz, CH), 6.17–6.07 (m, 2H, CH and =CH), 2.38 (s, 3H, CH_3). **^{13}C NMR (d6-acetone, 100 MHz):** δ 143.7 (C_{Ar}), 139.3 (C_{Ar}), 136.6 (C_{Ar}), 133.1 (C_{Ar}), 129.2 (CH), 128.9 (C_{Ar}), 128.4 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 125.0 (CH), 56.9 (CH), 20.5 (CH). **MS (ESI): m/z ($C_{22}H_{19}NO_2S$ + H$^+$) found:** 362.1.

2-(4-Chlorophenyl)-1-tosyl-1,2-dihydroquinoline **171c**[4a]



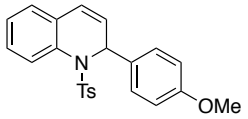
Colourless crystalline solid (70 mg, 88% yield); m.p. 135–137 °C. Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.64 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.32 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.28 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.19–7.21 (m, 3H, H_{Ar}), 7.08–7.16 (m, 3H, H_{Ar}), 6.97 (dd, 1H, *J* = 7.5, 1.0 Hz, H_{Ar}), 6.30 (d, 1H, *J* = 9.5 Hz, CH), 5.98 (d, 1H, *J* = 6.0 Hz, CH), 5.85 (dd, 1H, *J* = 9.5, 6.0 Hz. CH), 2.35 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.7 (C_{Ar}), 137.0 (C_{Ar}), 136.1 (C_{Ar}), 133.9 (C_{Ar}), 132.8 ($C_{Ar}H$), 129.3 (CH), 129.0 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 126.1 ($C_{Ar}H$), 126.0 (CH), 56.3 (CH), 21.7 (CH). **MS (ESI): m/z ($C_{22}H_{18}NClO_2S$ + H^+) found:** 396.1 and 398.1.

2-(4-Bromophenyl)-1-tosyl-1,2-dihydroquinoline **171d**[4a]



Colourless oil (82 mg, 93% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.64 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.31–7.37 (m, 4H, H_{Ar}), 7.20–7.22 (m, 3H, H_{Ar}), 7.08–7.14 (m, 3H, H_{Ar}), 6.97 (dd, 1H, *J* = 7.5, 1.0 Hz, H_{Ar}), 6.30 (d, 1H, *J* = 9.5 Hz, CH), 5.97 (d, 1H, *J* = 6.0 Hz, CH), 5.85 (dd, 1H, *J* = 9.5, 6.0 Hz, CH), 2.35 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.7 (C_{Ar}), 137.6 (C_{Ar}), 136.1 (C_{Ar}), 132.8 (C_{Ar}), 131.7 ($C_{Ar}H$), 129.3 (CH), 128.6 ($C_{Ar}H$), 128.6 (C_{Ar}), 127.7 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.5 (CH), 126.1 ($C_{Ar}H$), 125.9 ($C_{Ar}H$), 122.1 (CH), 56.4 (CH), 21.7 (CH_3). **MS (ESI): m/z ($C_{22}H_{18}NBrO_2S$ + H^+) found:** 440.0 and 442.0.

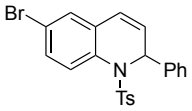
2-(4-Methoxyphenyl)-1-tosyl-1,2-dihydroquinoline **171e**[4b]



Colourless oil (56 mg, 71% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 7.62 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.32 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.18–7.25 (m,

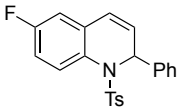
3H, H_{Ar}), 7.08–7.14 (m, 3H, H_{Ar}), 6.97 (d, 1H, *J* = 7.5 Hz, H_{Ar}), 6.76 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.27 (d, 1H, *J* = 9.5 Hz, CH), 5.97 (d, 1H, *J* = 6.0 Hz, CH), 5.84 (dd, 1H, *J* = 9.5, 6.0 Hz, CH), 3.73 (d, 3H, CH_3), 2.35 (d, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 159.5 (C_{Ar}), 143.5 (C_{Ar}), 136.4 ($C_{Ar}H$), 132.9 ($C_{Ar}H$), 130.4 (CH), 129.2 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 125.5 (CH), 113.9 ($C_{Ar}H$), 56.8 (CH), 55.3 (CH_3), 21.7 (CH_3). **MS (ESI): m/z ($C_{23}H_{21}NO_3S$ + H^+) found:** 392.1.

6-Bromo-2-phenyl-1-tosyl-1,2-dihydroquinoline **171f**



Pale yellow oil (56 mg, 64% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.52 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 7.36 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.31 (dd, 3H, *J* = 8.5, 2.0 Hz, H_{Ar}), 7.22–7.24 (m, 3H, H_{Ar}), 7.12–7.14 (m, 3H, H_{Ar}), 6.23 (d, 1H, *J* = 9.5 Hz, CH), 6.02 (d, 1H, *J* = 6.0 Hz, CH), 5.93 (dd, 1H, *J* = 9.5, 6.0 Hz, CH), 2.37 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.9 ($C_{Ar}Br$), 138.0 (C_{Ar}), 136.1 (C_{Ar}), 132.1 (C_{Ar}), 131.2 (CH), 130.4 (C_{Ar}), 129.5 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 124.7 (CH), 120.0 (C_{Ar}), 57.1 (CH), 21.7 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3062, 2922, 1644, 1598, 1484, 1343, 1089, 813, 685. **MS (ESI) m/z calcd. ($C_{22}H_{18}BrNO_2S$ + Na^+):** 462.0134 & 464.0119, **found:** 462.0137 & 464.0124 (M + Na^+).

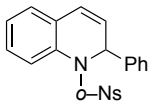
6-Fluoro-2-phenyl-1-tosyl-1,2-dihydroquinoline **171g**



Colourless oil (61 mg, 81% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.52 (m, 1H, H_{Ar}), 7.15–7.23 (m, 7H, H_{Ar}), 7.04 (d, 2H, *J* = 7.5 Hz, H_{Ar}), 6.82 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 6.60 (d, 1H, *J* = 8.5 Hz, H_{Ar}), 6.14 (d, 1H, *J* = 9.5 Hz, CH), 5.94 (d, 1H, *J* = 5.5 Hz, CH), 5.83–5.85 (m, 1H, CH), 2.29 (s, 3H, CH^3). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 161.0 (d, *J* = 246 Hz, $C_{Ar}F$), 143.8 (C_{Ar}), 137.9 (C_{Ar}), 136.0 (C_{Ar}), 130.4 (d, *J* = 9 Hz, C_{Ar}), 129.8 (d, *J* = 9 Hz, $C_{Ar}H$), 129.3 (CH), 128.8 (d,

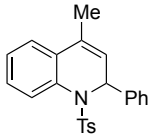
J = 3 Hz, C_{Ar}), 128.6 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 125.0 (CH), 115.1 (d, *J* = 23 Hz, $C_{Ar}H$), 112.7 (d, *J* = 23 Hz, $C_{Ar}H$), 57.1 (CH), 21.7 (CH). **^{19}F NMR ($CDCl_3$, 282 MHz)** δ –115.2. **IR (neat, ν_{max}, cm^{-1}):** 3062, 3031, 2962, 2924, 1612, 1598, 1578, 1484, 1451, 1345, 1262, 1165, 1045, 810, 709, 576. **MS (ESI) m/z calcd. ($C_{22}H_{18}FNO_2S + Na^+$):** 402.0934, **found:** 402.0938 ($M + Na^+$).

1-((2-Nitrophenyl)sulfonyl)-2-phenyl-1,2-dihydroquinoline 171h



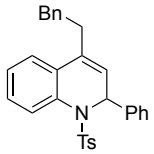
Colourless oil (51 mg, 65% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.65 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.59 (td, 1H, *J* = 8.0, 1.0 Hz, H_{Ar}), 7.48 (dd, 1H, *J* = 8.0, 1.0 Hz, H_{Ar}), 7.29–7.36 (m, 3H, H_{Ar}), 7.17–7.25 (m, 6H, H_{Ar}), 7.05 (dd, 1H, *J* = 7.0, 2.0 Hz, H_{Ar}), 6.36 (d, 1H, *J* = 10.0 Hz, CH), 6.17 (m, 1H, CH), 6.10 (d, 1H, *J* = 6.0 Hz, CH); **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 137.6, (C_{Ar}), 133.8 ($C_{Ar}H$), 132.0 (C_{Ar}), 131.1 (C_{Ar}), 130.7 ($C_{Ar}H$), 130.7 (C_{Ar}), 129.5 (CH), 129.2 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 125.0 (CH), 123.7 ($C_{Ar}H$), 57.3 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3088, 3062, 2960, 2925, 1679, 1603, 1542, 1371, 1265, 1173, 1060, 1023, 766, 697, 584. **MS (ESI) m/z calcd. ($C_{21}H_{16}N_2O_4S + Na^+$):** 415.0723, **found:** 415.0722 ($M + Na^+$).

4-Methyl-2-phenyl-1-tosyl-1,2-dihydroquinoline 171i [4b]



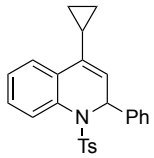
Colourless oil (60 mg, 80% yield). Acquired analytical data matches that reported in the literature. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.61 (d, 1H, *J* = 7.5 Hz, H_{Ar}), 7.05–7.28 (m, 12H, H_{Ar}), 5.90 (d, 1H, *J* = 6.0 Hz, CH), 5.62 (d, 1H, *J* = 6.0 Hz, CH), 2.34 (s, 3H, CH_3), 1.72 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.2 (C_{Ar}), 138.8 (C_{Ar}), 135.9 (C_{Ar}), 133.0 (C_{Ar}), 131.2 ($C_{Ar}H$), 130.8 (C_{Ar}), 128.9 (CH), 128.3 ($C_{Ar}H$), 128.18 ($C_{Ar}H$), 128.08 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 123.08 ($C_{Ar}H$), 122.99 (CH), 56.7 (CH), 21.5 (CH_3), 17.9 (CH). **MS (ESI): m/z ($C_{23}H_{21}NO_2S + Na^+$) found:** 398.1.

4-Phenethyl-2-phenyl-1-tosyl-1,2-dihydroquinoline 171j



Colourless crystalline solid (71 mg, 76% yield); T_m = 135–137 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.68 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.34 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.27–7.31 (m, 4H, H_{Ar}), 7.15–7.24 (m, 7H, H_{Ar}), 7.11 (d, 4H, *J* = 8.0 Hz, H_{Ar}), 6.00 (d, 1H, *J* = 6.0 Hz, CH), 5.76 (d, 1H, *J* = 6.0 Hz, CH), 2.44–2.46 (m, 3H, CH), 2.32 (s, 3H, CH_3), 2.13–2.15 (m, 1H, CH); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.5 (C_{Ar}), 141.7 (C_{Ar}), 138.7 (C_{Ar}), 136.5 (C_{Ar}), 135.2 (C_{Ar}), 133.4 (C_{Ar}), 129.9 (C), 129.2 ($C_{Ar}H$), 128.74 ($C_{Ar}H$), 128.68 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 123.0 ($C_{Ar}H$), 122.7 (CH), 56.8 (CH), 34.5 (CH_2), 33.6 (CH_2), 21.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3060, 3023, 2923, 2851, 1643, 1596, 1490, 1451, 1342, 1163, 1087, 1032, 976, 808, 682, 570, 544. **MS (ESI) m/z calcd. ($C_{30}H_{27}NO_2S$ + Na^+):** 488.1655, **found:** 488.1655 (M + Na^+).

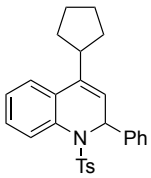
4-Cyclopropyl-2-phenyl-1-tosyl-1,2-dihydroquinoline 171k



Orange solid (59 mg, 73% yield); T_m = 116–118 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.55 (dd, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 7.40 (dd, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 7.11–7.21 (m, 10H, H_{Ar}), 7.01 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 5.89 (d, 1H, *J* = 6.0 Hz, CH), 5.55 (dd, 1H, *J* = 6.0, 1.5 Hz, CH), 2.28 (s, 3H, CH_3), 1.30–1.32 (m, 1H, CH), 0.65–0.67 (m, 1H, CH), 0.44–0.47 (m, 1H, CH), 0.10–0.14 (m, 1H, CH), –0.30–0.33 (m, 1H, CH). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.5 (C_{Ar}), 138.8 (C_{Ar}), 136.8 (C_{Ar}), 136.2 (C_{Ar}), 132.9 (C_{Ar}), 130.9 (C), 129.1 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 123.7 ($C_{Ar}H$), 121.9 (CH), 56.8 (CH), 21.6 (CH_3), 11.9 (CH), 6.2 (CH_2), 4.3 (CH_2), 1.2 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3063, 3030, 2920, 2851, 1736, 1638, 1599,

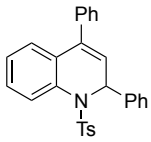
1449, 1345, 1163, 1008, 782, 698, 575. **MS (ESI) m/z calcd. ($C_{25}H_{23}NO_2S + Na^+$):** 424.1342, **found:** 424.1342 ($M + Na^+$).

4-Cyclopentyl-2-phenyl-1-tosyl-1,2-dihydroquinoline **171l**



Pale yellow oil (41 mg, 45% yield). **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 7.64 (d, 1H, J = 7.5 Hz, H_{Ar}), 7.15–7.22 (m, 6H, H_{Ar}), 7.28–7.33 (m, 4H, H_{Ar}), 7.08 (d, 1H, J = 8.0 Hz, H_{Ar}), 5.99 (d, 1H, J = 6.5 Hz, CH), 5.71 (dd, 1H, J = 6.5, 1.5 Hz, CH), 2.77–2.83 (m, 1H, CH), 2.33 (s, 3H, CH_3), 1.80–1.86 (m, 1H, CH), 1.58–1.64 (m, 2H, CH), 1.48–1.54 (m, 2H, CH), 1.34–1.42 (m, 2H, CH), 0.33–0.38 (m, 1H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 143.4 (C_{Ar}), 139.3 (C_{Ar}), 138.9 (C_{Ar}), 136.6 (C_{Ar}), 133.2 (C_{Ar}), 130.8 (C), 129.2 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.5 ($C_{Ar}H$), 123.7 ($C_{Ar}H$), 119.7 (CH), 56.9 (CH), 39.8 (CH), 31.9 (CH_2), 31.2 (CH_2), 25.4 (CH_2), 25.0 (CH_2), 21.6 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3061, 2955, 2916, 2866, 1598, 1492, 1450, 1348, 1165, 1053, 809, 755, 704. **MS (ESI) m/z calcd. (**$C_{27}H_{27}NO_2S$ **+ Na$^+$):** 452.1655, **found:** 452.1659 ($M + Na^+$).

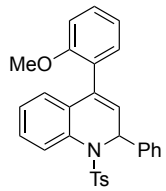
2,4-Diphenyl-1-tosyl-1,2-dihydroquinoline **171m**



Colourless crystalline solid (51 mg, 55% yield); T_m = 195–197 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.71 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.38 (t, 4H, J = 8.5 Hz, H_{Ar}), 7.27–7.30 (m, 4H, H_{Ar}), 7.24–7.25 (m, 3H, H_{Ar}), 7.03–7.11 (m, 3H, H_{Ar}), 6.84–6.88 (m, 3H, H_{Ar}), 6.18 (d, 1H, J = 6.5 Hz, CH), 5.89 (d, 1H, J = 6.5 Hz, CH), 2.31 (s, 3H, CH_3); **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.6 (C_{Ar}), 138.7 (C_{Ar}), 138.4 (C_{Ar}), 138.3 (C_{Ar}), 136.0 (C_{Ar}), 133.4 (C), 130.3 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 128.79 ($C_{Ar}H$), 128.76 ($C_{Ar}H$), 128.64 ($C_{Ar}H$), 128.60 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.71 ($C_{Ar}H$), 127.65 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 125.9 ($C_{Ar}H$), 124.4 (C),

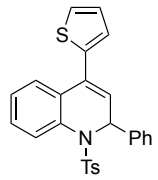
56.8 (CH), 21.5 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3058, 3031, 2917, 2849, 1738, 1594, 1491, 1329, 1151, 1062, 988, 805, 753. **MS (ESI) m/z calcd. ($C_{28}H_{23}NO_2S + Na^+$):** 460.1342, **found:** 460.1333 ($M + Na^+$).

4-(2-Methoxyphenyl)-2-phenyl-1-tosyl-1,2-dihydroquinoline 171n



Off-white solid (86 mg, 92% yield); T_m = 203–205 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.67 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.56 (d, 2H, *J* = 7.0 Hz, H_{Ar}), 7.09–7.48 (m, 10H, H_{Ar}), 7.01 (t, 1H, *J* = 7.5 Hz, H_{Ar}), 6.93 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 6.86 (m, 1H, H_{Ar}), 6.67 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 6.15 (d, 1H, *J* = 6.0 Hz, CH), 5.89 (d, 1H, *J* = 6.0 Hz, CH), 3.71 (brs, 3H, OCH_3), 2.38 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 157.5 (C_{Ar}), 143.4 (C_{Ar}), 132.8 (C_{Ar}), 130.8 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.2 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.3 (C_{Ar}), 125.8 ($C_{Ar}H$), 125.6 ($C_{Ar}H$), 120.3 ($C_{Ar}H$), 111.1 (CH), 57.0 (CH_3), 55.5 (CH), 21.6 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3067, 3027, 2917, 1580, 1492, 1351, 1254, 1162, 988, 787, 700, 565. **MS (ESI) m/z calcd. ($C_{29}H_{25}NO_3S + Na^+$):** 490.1447, **found:** 490.1438 ($M + Na^+$).

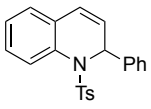
2-Phenyl-4-(thiophen-2-yl)-1-tosyl-1,2-dihydroquinoline 171o



Black solid (54 mg, 61% yield); T_m = 158–160 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** δ 7.70 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.34–7.37 (m, 4H, H_{Ar}), 7.15–7.30 (m, 9H, H_{Ar}), 7.06 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.99 (dd, 1H, *J* = 5.0, 3.5 Hz, H_{Ar}), 6.69 (dd, 1H, *J* = 3.5, 1.0 Hz), 6.14 (d, 1H, *J* = 6.5 Hz, CH), 6.01 (d, 1H, *J* = 6.5 Hz, CH), 2.27 (s, 3H, CH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 143.7 (C_{Ar}), 139.6 (C_{Ar}), 138.0 (C_{Ar}), 135.7 (C_{Ar}), 133.4 (C_{Ar}), 131.6 (C_{Ar}), 129.8 (C_{Ar}), 129.4 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 126.8 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 125.6 ($C_{Ar}H$), 125.3

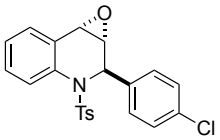
(CH), 56.7 (CH), 21.6 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3062, 3029, 2922, 2853, 1623, 1598, 1449, 1347, 1164, 1089, 1062, 808, 698, 566. **MS (ESI) m/z calcd. ($C_{26}H_{21}NO_2S_2 + Na^+$):** 466.0906, **found:** 466.0910 ($M + Na^+$).

Experimental procedure for the preparation of 2-phenyl-1-tosyl-1,2-dihydroquinoline 171b mediated by chiral Brønsted acid BA21.



To a solution of toluene (2 mL) containing **169b** (23 mg, 0.06 mmol) was added **BA21** (2 mg, 0.003 mmol) in one portion at 0 °C. On monitoring the reaction mixture to completion by TLC analysis after 2 h, the solvent was removed under reduced pressure and the resulting crude mixture was purified by column chromatography on silica gel (eluent: 10:1 *n*Hexane-EtOAc) to afford the title compound. Colourless oil (19 mg, 89% yield). Enantiomeric excess is 35% as determined by chiral HPLC (Daicel Chiralpak IC column, 85:15 *n*–hexane–*i*PrOH, flow rate = 1.0 mL/min, 254 nm): major isomer: t_R = 15.3 min; minor isomer: t_R = 13.4 min.

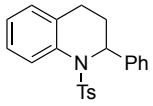
Experimental procedure for the preparation of 2-(4-chlorophenyl)-3-tosyl-1a,2,3,7b-tetrahydrooxireno[2,3-c]quinoline 227



To a solution of dichloromethane (5 mL) containing **171c** was added $NaHCO_3$ (5 mg, 0.06 mmol) and *m*-CPBA (10 mg, 0.06 mmol) in one portion at 0 °C. On monitoring the reaction mixture to completion by TLC analysis after 6 h, the solvent was removed under reduced pressure and the resulting crude mixture was purified by column chromatography on silica gel (eluent: 5:1 *n*–hexane–EtOAc) to afford the title compound. Colourless oil (22 mg, 85% yield). **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 7.74 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.48 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.30–7.35 (m, 2H, H_{Ar}), 7.14–7.25 (m, 7H, H_{Ar}), 5.87 (d, 1H, *J* = 2.0 Hz, CH), 3.89–3.97 (m, 1H ,CH), 3.81 (d, 1H, *J* = 4.0 Hz, CH), 2.37 (s, 3H ,CH_3). **^{13}C NMR**

($CDCl_3$, 125 MHz): δ 143.7 (C_{Ar}), 135.7 (C_{Ar}), 135.1 (C_{Ar}), 134.5 (C_{Ar}), 133.6 ($C_{Ar}Cl$), 130.1 ($C_{Ar}H$), 129.9 ($C_{Ar}H$), 129.2 ($C_{Ar}H$), 129.13 ($C_{Ar}H$), 129.10 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 126.4 (C_{Ar}), 126.1 (CH), 62.1 (CH), 55.0 (CH), 50.8 (CH), 21.8 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3069, 3032, 2923, 1598, 1491, 1343, 1162, 1091, 976, 807, 760, 676, 569, 547. **MS (ESI) m/z calcd. ($C_{22}H_{18}ClNO_3S + Na^+$):** 434.0588 & 436.0564 **found:** 434.0590 & 436.0579 ($M + Na^+$).

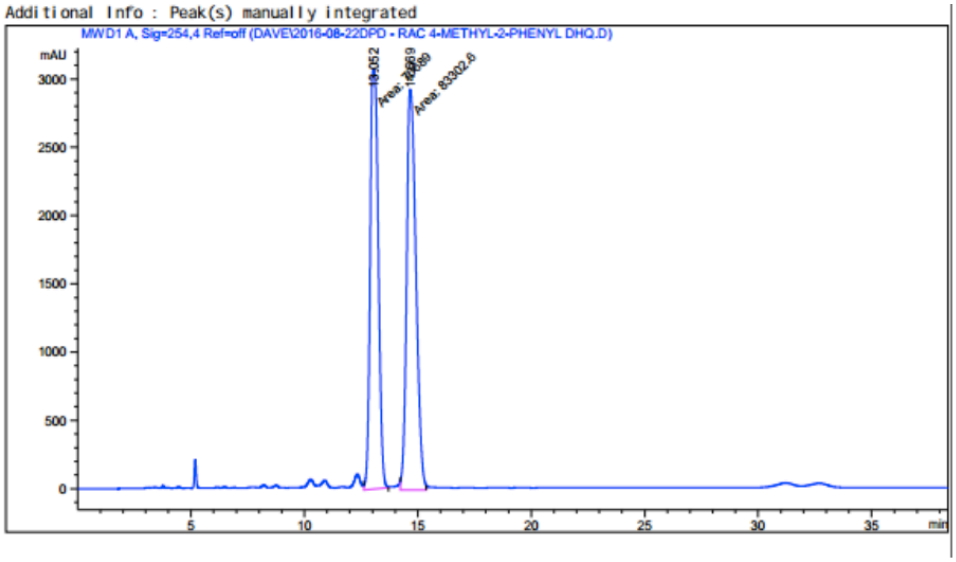
Experimental procedure for the preparation of 2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline 228



To a round bottom flask containing Pd/C (0.10 g, 10 wt. %) in methanol (5 mL) and previously purged three times with nitrogen gas was added **171c** (0.025 g, 0.06 mmol) dissolved in methanol (5 mL). A hydrogen atmosphere was then purged into the stirring solution and the resulting reaction mixture was stirred at room temperature for 2 h. Upon completion, the reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by column chromatography on silica gel (eluent: 5:1 *n*–hexane–EtOAc) gave the title compound. Pale yellow oil (21 mg, 95% yield). **^{1}H NMR ($CDCl_3$, 500 MHz):** δ 7.87 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.43 (d, 2H, J = 6.0 Hz, H_{Ar}), 7.28–7.31 (m, 5H, H_{Ar}), 7.18–7.22 (m, 3H, H_{Ar}), 7.10 (t, 1H, J = 7.5 Hz, H_{Ar}), 6.96 (d, 1H, J = 7.5 Hz, H_{Ar}), 5.36 (brs, 1H, CH), 2.39 (s, 3H, CH_3), 2.31–2.34 (m, 1H, CH_2), 2.18 (brs, 1H, CH_2), 1.79–1.88 (m, 2H, CH_2). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 143.6 (C_{Ar}), 142.6 (C_{Ar}), 136.4 (C_{Ar}), 136.3 (C_{Ar}), 134.1 ($C_{Ar}H$), 129.6 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 59.8 (CH), 32.1 (CH_2), 25.5 (CH_2), 21.7 (CH_3). **IR (neat, ν_{max}, cm^{-1}):** 3030, 2950, 2869, 1599, 1487, 1454, 1346, 1162, 1090, 972, 813, 794, 699, 660, 570. **MS (ESI) m/z calcd. ($C_{22}H_{21}NO_2S + Na^+$):** 386.1185, **found:** 386.1187 ($M + Na^+$).

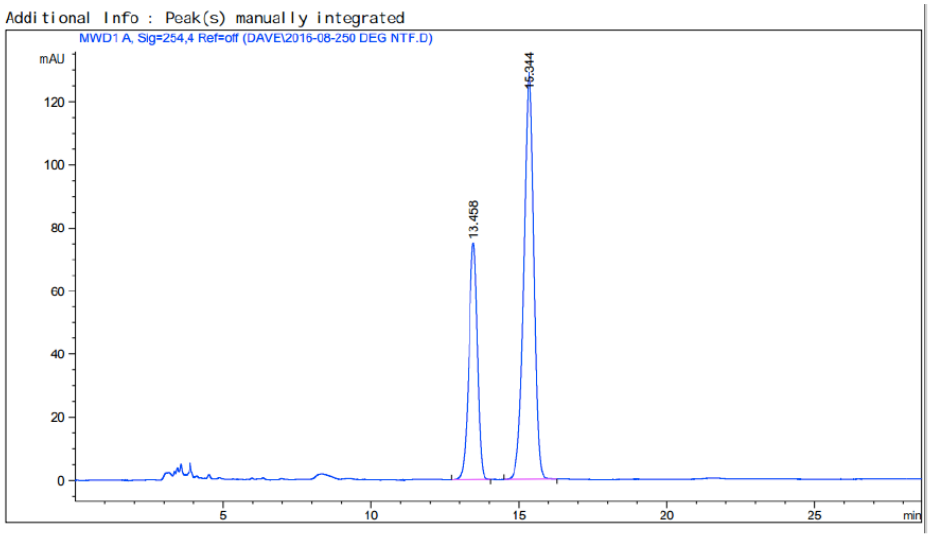
Chromatographs of 2-phenyl-1-tosyl-1,2-dihydroquinoline **171b**

HPLC resolution data were collected using a Daicel Chiralpak IC column, 85:15 *n*–hexane–*i*PrOH, flow rate = 1.0 mL/min, 254 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.052	MM	0.4154	7.66890e4	3076.63989	47.9331
2	14.669	MM	0.4729	8.33026e4	2935.74194	52.0669

Figure 6.1: Racemic sample of 2-phenyl-1-tosyl-1,2-dihydroquinoline **171b**



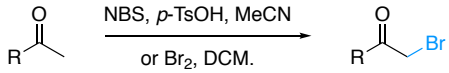
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.458	BB	0.3084	1490.64990	74.98819	32.6687
2	15.344	BB	0.3659	3072.28540	129.00035	67.3313

Figure 6.2: Chiral trace for 2-phenyl-1-tosyl-1,2-dihydroquinoline **171b**

6.5 Experimental Data for Chapter 4

6.5.1 General Procedures

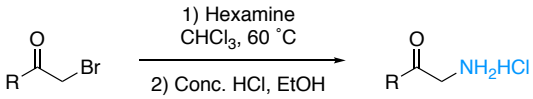
α–Bromination – to access the *α*–bromo ketone **245**



α–Bromination with NBS: To a solution of the appropriate ketone (30 mmol) in MeCN (4.5 mL/mmol) at RT was added NBS (1.15 eq.), and *p*-TsOH (0.1 eq.). The resulting mixture was brought to reflux and allowed to stir for 12 h, or until completion as determined by TLC analysis. Upon completion Et_2O (3 mL/mmol) was added and the solution washed with water (3 x 3 mL/mmol), and saturated $NaHCO_3$ (3 mL/mmol). The combined organics were then dried over $MgSO_4$ and the mixture concentrated under reduced pressure. The resulting solid residue was then recrystallised with a mixture of *n*-hexane and EtOAc *circa*. 6:1.

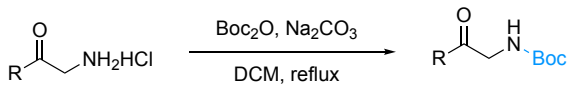
α–Bromination with Br_2: To a solution of the appropriate ketone (30 mmol) in DCM (4.5 mL/mmol) in an ice bath was added, dropwise, Br_2 (1 eq.). The resulting mixture was kept below 3 °C and allowed to stir for 2 h, or until completion as determined by TLC analysis. Upon completion, water (3 mL/mmol) was added and the solution stirred for a further 4 h. The resulting mixture was extracted with EtOAc/*n*Hexane 3:1 (3 x 3 mL/mmol), sat. $NaHCO_3$ (3 mL/mmol), and saturated brine (3 mL/mmol). The combined organics were then dried over $MgSO_4$ and the mixture concentrated under reduced pressure.

Amination – to access the NH_2.HCl salt **246**



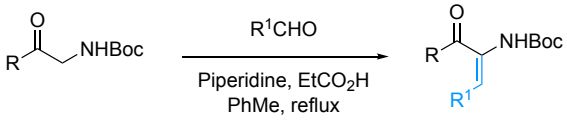
To a solution of hexamethylenetetramine (1.1 eq.) in $CHCl_3$ (3 mL/mmol) was added the appropriate bromo-ketone (10 mmol). The mixture was then brought to reflux and stirred vigorously for 4 h, or until completion as determined by TLC analysis. Upon completion the reaction mixture was cooled to RT and filtered. The collected precipitate was then suspended in EtOH (2 mL/mmol) and conc. HCl (1 mL/mmol) was added dropwise. The solution was then stirred at RT for 12 h. The resulting white precipitate was then removed *via* filtration and the filtrate collected and concentrated under reduced pressure.

t-Butoxycarbonyl group installation to **247**



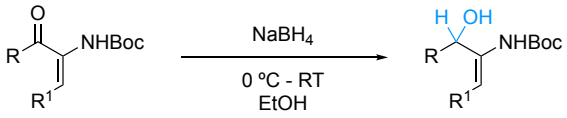
To a solution of the appropriate amino HCl salt (16 mmol), Boc_2O (1.5 eq.) in DCM (3 mL/mmol) was added Na_2CO_3 (1.5 eq.) and the resulting mixture brought to reflux and stirred for 16 h, or until completion as determined by TLC analysis. Upon completion the reaction mixture was cooled to RT and Et_2O (3 mL/mmol) was added to dilute the suspension. The solution was then washed with water (3 x 3 mL/mmol) and sat. brine (3 mL/mmol). The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: *circa*. 15% EtOAc–*n*–hexane).

Condensation reaction – to access *α,β*-unsaturated ketone **248**



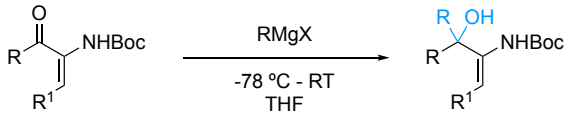
Under nitrogen atmosphere, to an anhydrous toluene (10 mL) solution of the appropriate acetamide (6 mmol), aldehyde (1.2 eq.), and propionic acid (0.2 eq.) was added piperidine (0.1 eq.). The resulting mixture was then stirred and heated to reflux for 16 h. The reaction mixture was then allowed to cool to room temperature. The resulting precipitate was filtered, dried *in vacuo*, and used in the next step without further purification.

Sodium borohydride reduction – to access secondary allylic alcohols **172**



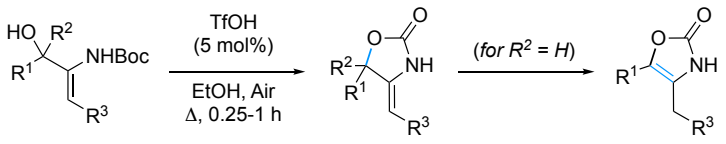
The appropriate ketone (1 mmol) was dissolved in EtOH (30 mL/mmol) and cooled to 0 °C. Sodium borohydride (3 eq.) was added in one portion and the reaction mixture was allowed to stir for 2 h. Upon completion, the reaction mixture was quenched by the addition of water (1 mL/mmol) and the solvent was removed under reduced pressure. The crude mixture was dissolved in DCM (10 mL/mmol), washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (eluent: 40% EtOAc-*n*Hexane) to afford the secondary alcohol substrate.

Grignard addition – to access tertiary allylic alcohols **172**



The appropriate ketone (1 mmol) was dissolved in THF (60 mL/mmol) and a solution of alkyl or aryl magnesium bromide (4.5 eq.) was added at -78 °C and subsequently allowed to return to room temperature. The reaction mixture was allowed to stir at room temperature for 12 h and the progress of the reaction was followed by TLC analysis and mass spectrometry. Upon completion, the reaction mixture was quenched with saturated NH_4Cl (60 mL/mmol). After additional stirring at room temperature for 10 min, EtOAc (90 mL/mmol) was added and the organic phase was separated. The aqueous phase was further extracted with EtOAc (3 x 30 mL/mmol) and the combined organic layers were washed with brine (60 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (eluent: 40% EtOAc-*n*Hexane) to afford the tertiary alcohol substrate.

Brønsted acid-catalysed cyclisation of *β*–amino enols **174** and **175**



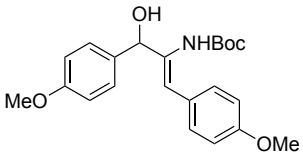
169 **175** **174**

To a 2 mL round bottomed flask was added the appropriate β-amino enol (0.1 mmol) and a 1 mL solution of TfOH in EtOH (0.005 mmol/mL) in one portion. The reaction mixture was brought to reflux and allowed to stir for 0.25-1 h whilst the progress of the reaction was followed by TLC analysis. Upon completion, the reaction mixture was quenched with water (20 mL/mmol) and the product extracted with EtOAc (3 x 5

mL). The combined organics were then washed with saturated brine (100 mL/mmol), dried over $MgSO_4$ and subsequently concentrated under reduced pressure. The resulting residue was then purified using column chromatography (15% EtOAc–*n*–hexane) to afford the oxazol-2(3*H*)-one **174** or oxazolidin-2-one **175**.

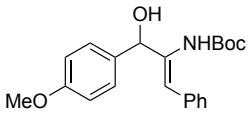
6.5.2 Compound Data

t-Butyl (3-hydroxy-1,3-bis(4-methoxyphenyl)prop-1-en-2-yl)carbamate **172a**



White solid (3.1 g, 77% yield); T_m = 94–96 °C. **^{1}H NMR (CDCl$_3$, 400 MHz)**: δ 7.34 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.28 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.92-6.86 (m, 4H, H_{Ar}), 6.21 (brs, 1H, NH), 6.12 (s, 1H, C=CH), 5.41 (s, 1H. OCH), 5.25 (brs, 1H, OH), 3.76 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 1.34 (brs, 9H, CCH_3). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 158.8 (C_{Ar}), 158.7 (C_{Ar}), 154.3 (HNCOO), 135.4 (C_{Ar}), 133.4 ($C_{Ar}H$), 129.8 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.4 ($C_{Ar}H$), 118.9 (=CH), 114.0 ($C_{Ar}H$), 113.4 ($C_{Ar}H$), 80.8 (C), 75.6 (CH), 55.2 (OCH_3), 28.0 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3007, 2967, 1694, 1606, 1507, 1288, 1248, 1170, 1024, 890, 811, 771, 681. **MS (ESI) m/z calcd. ($C_{22}H_{27}NO_5$ + Na^+) calcd.:** 408.1787, **found:** 408.1783 (M + Na^+).

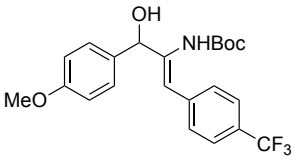
t-Butyl (3-hydroxy-3-(4-methoxyphenyl)-1-phenylprop-1-en-2-yl)carbamate **172b**



White solid (98 mg, 88% yield); T_m = 85–98 °C. **^{1}H NMR (CDCl$_3$, 400 MHz)**: δ 7.33-7.38 (m, 6H, H_{Ar}), 7.23-7.27 (m, 1H, H_{Ar}), 6.88 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.25 (brs, 1H, NH), 6.09 (s, 1H, C=CH), 5.51 (d, 1H, *J* = 7.5 Hz, OCH), 5.18 (brs, 1H, NH), 3.81 (s, 3H, OCH_3), 1.34 (brs, 9H, CCH_3). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 159.0 (C_{Ar}), 154.3 (HNCOO), 135.3 (C_{Ar}), 133.5 (C_{Ar}), 128.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 113.6 (=CH), 81.3 (C), 75.5 (OCH), 55.4 (OCH_3), 28.2 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 2999, 2845, 1686,

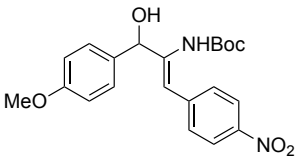
1524, 1230, 1151, 1015, 885, 803, 733, 680. **MS (ESI) m/z calcd. ($C_{21}H_{25}NO_4 + Na^+$) calcd.:** 378.1681, **found:** 378.1675 ($M + Na^+$).

t-Butyl (3-hydroxy-3-(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-1-en-2-yl)carbamate 172c



White solid (108 mg, 87% yield); T_m = 88–90 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.56 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.44 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.34 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.86 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.05-6.30, (m, 2H), 5.47 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 1.31 (s, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 159.2 (C_{Ar}), 153.6 (HNCOO), 139.3 (C_{Ar}), 138.8 (C_{Ar}), 132.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 125.5 ($C_{Ar}H$), 124.2 (q, J = 272.5 Hz, CF_3), 113.5 (=CH), 81.4 (C), 75.2 (OCH), 55.3 (OCH_3), 28.0 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3445, 3260, 2988, 2936, 1702, 1612, 1507, 1323, 1242, 1158, 1109, 1067, 1014, 827, 752. **MS (ESI) m/z calcd. ($C_{22}H_{24}F_3NO_4$ - H^+):** 422.1579, **found:** 422.1581 ($M - H^+$).

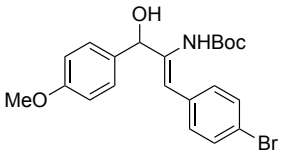
t-Butyl (3-hydroxy-3-(4-methoxyphenyl)-1-(4-nitrophenyl)prop-1-en-2-yl)carbamate 172d



Yellow solid (121 mg, 74% yield); T_m = 126–130 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 8.15 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.48 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.34 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.88 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.09-6.30 (m, 2H), 5.48 (d, 1H, *J* = 4.0 Hz, OCH), 3.79 (s, 3H, CH_3), 1.31 (brs, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 159.4 (C_{Ar}), 153.1 (HNCOO), 146.3 (C_{Ar}), 142.8 (C_{Ar}), 140.1 (C_{Ar}), 132.5 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 123.9 ($C_{Ar}H$), 113.9 (=CH), 81.7 (C), 75.2 (OCH), 55.4 (OCH_3), 28.1 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3005, 2977, 2904, 1697, 1510, 1286, 1250, 1169,

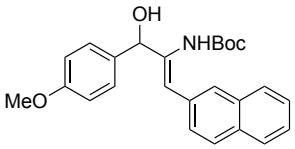
1033, 691. **MS (ESI) m/z calcd. ($C_{21}H_{24}N_2O_6$ - H^+):** 399.1556, **found:** 399.1567 (M - H^+).

t-Butyl (1-(4-bromophenyl)-3-hydroxy-3-(4-methoxyphenyl)prop-1-en-2-yl)carbamate 172e



White solid (106 mg, 87% yield). T_m = 92–94 °C. **^{1}H NMR ($CDCl_3$, 500 MHz)**: ∂ 7.47 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.35 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.21 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.88 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 5.96-5.18 (m, 2H), 5.48 (s, 1H, OCH), 4.42 (brs, 1H, OH), 3.80 (s, 3H, OCH_3), 1.34 (brs, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 125 MHz)**: ∂ 159.2 (C_{Ar}), 153.9 (HNCOO), 134.3 (C_{Ar}), 133.1 (C_{Ar}), 131.9 (C_{Ar}), 130.3 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 121.2 ($C_{Ar}H$), 113.7 ($C_{Ar}H$), 81.5 (=CH), 75.4 (C), 55.4 (OCH), 28.2 (OCH_3). **IR (neat, ν_{max}/cm^{-1})**: 3456, 3251, 2926, 1715, 1509, 1345, 1261, 1171, 1111, 1055, 1019, 759. **MS (ESI) m/z calcd. ($C_{21}H_{24}NO_4Br$ + Na^+)**: 456.0786 & 458.0766, **found**: 456.0780 & 458.0759 (M + Na^+).

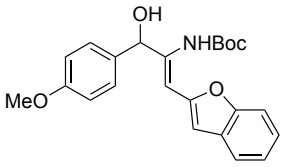
t-Butyl (3-hydroxy-3-(4-methoxyphenyl)-1-(naphthalen-2-yl)prop-1-en-2-yl)carbamate 172f



Yellow solid (95 mg, 86% yield); T_m = 120–124 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.77–7.81 (m, 4H, H_{Ar}), 7.46–7.52 (m, 3H, H_{Ar}), 7.42 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.90 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.37 (brs, 1H, NH), 6.32 (s, 1H, C=CH), 5.55 (s, 1H, OCH), 3.79 (s, 3H, OCH_3), 1.36 (brs, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.9 (C_{Ar}), 154.1 (HNCOO), 137.4 ($C_{Ar}H$), 133.4 ($C_{Ar}H$), 133.4 ($C_{Ar}H$), 132.9 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 126.4 ($C_{Ar}H$), 118.7 ($C_{Ar}H$), 113.5 (=CH), 81.0 (C), 75.4 (OCH), 55.2 (OCH_3), 28.0 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 2979, 2837, 1692, 1507, 1244, 1156, 1024, 905,

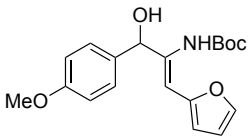
815, 747, 671. **MS (ESI) m/z calcd. ($C_{25}H_{27}NO_4$ - OH^+):** 388.1913, **found:** 388.1903 (M - OH^+).

t-Butyl (1-(benzofuran-2-yl)-3-hydroxy-3-(4-methoxyphenyl)prop-1-en-2-yl)carbamate 172g



Brown solid (86 mg, 91% yield); T_m = 108–112 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 8.26 (brs, 1H, NH), 7.49-7.51 (m, 1H, H_{Ar}), 7.44-7.46 (m, 1H, H_{Ar}), 7.40 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.27 (dt, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 7.22 (dt, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 6.90 (d, 2H, H_{Ar}), 6.51 (d, 1H, *J* = 0.5 Hz, C=CH), 5.72 (d, 1H, *J* = 7.0 Hz, H_{Ar}), 5.70 (s, 1H, OCH), 5.26 (brs, 1H, OH), 3.81 (s, 3H, OCH_3), 1.47 (s, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.9 (C_{Ar}), 154.2 (C_{Ar}), 153.5 (HNCOO), 153.4 (C_{Ar}), 140.1 (C_{Ar}), 133.2 (C_{Ar}), 128.2 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 124.4 ($C_{Ar}H$), 123.3 ($C_{Ar}H$), 120.8 ($C_{Ar}H$), 113.5 ($C_{Ar}H$), 110.8($C_{Ar}H$), 105.4($C_{Ar}H$), 101.6 (=CH), 81.6 (C), 73.7 (OCH), 55.3 (OCH_3), 28.2 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3491, 3396, 2977, 2933, 2837, 1715, 1490, 1446, 1242, 1149, 1021, 821, 731. **MS (ESI) m/z calcd. ($C_{23}H_{25}NO_5$ + Na^+):** 418.1630, **found:** 418.1597 (M + Na^+).

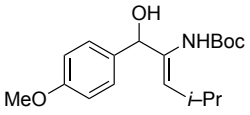
t-Butyl (1-(furan-2-yl)-3-hydroxy-3-(4-methoxyphenyl)prop-1-en-2-yl)carbamate 172h



Yellow oil (131 mg, 84% yield). **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.77 (brs, 1H), 7.39 (d, 1H, *J* = 2.0 Hz, H_{Ar}), 7.33 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.82–6.86 (m, 2H), 6.37 (dd, 1H, *J* = 3.5, 2.0 Hz), 6.17 (d, 1H, *J* = 3.5 Hz), 5.56 (brs, 1H), 5.60 (d, 1H, J = 7.0 Hz), 5.32 (brs, 1H), 3.76 (s, 3H), 1.40 (s, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.8 (C_{Ar}), 153.6 (HNCOO), 151.6 (C_{Ar}), 141.5 ($C_{Ar}H$), 136.8 ($C_{Ar}H$), 133.5 ($C_{Ar}H$), 127.6 ($C_{Ar}H$), 113.4 ($C_{HetAr}H$), 111.4 ($C_{HetAr}H$), 109.2 (=CH), 81.2 (C), 73.8 (OCH), 55.2 (OCH_3), 28.1 ($C(CH_3)_3$). **IR**

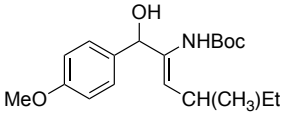
(neat, ν_{max}, cm^{-1}): 2933, 2837, 1685, 1604, 1508, 1366, 1245, 1155, 1020, 830, 767. **MS (ESI) m/z calcd. ($C_{19}H_{23}NO_5$ + Na^+):** 368.1452, **found:** 368.1474 (M + Na^+).

t-Butyl (1-hydroxy-1-(4-methoxyphenyl)-4-methylpent-2-en-2-yl)carbamate 172i



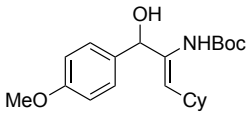
White solid (146 mg, 92% yield); T_m = 126–128 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.26 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.83 (d, 2H, *J* = 9.0 H, H_{Ar} z), 5.75 (brs, 1H), 5.20-5.23 (m, 2H), 4.91 (brs, 1H), 3.77 (s, 3H), 2.45-2.57 (m, 1H), 1.36 (s, 9H, CCH_3), 1.00 (t, 6H, *J* = 6.0 Hz). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.7 (C_{Ar}), 154.9 (HNCCOO), 133.9 (C_{Ar}), 133.6 (C_{Ar}H), 127.3 (C_{Ar}H), 113.4 (C), 80.4 (=CH), 75.8 (OCH), 55.2 (OCH_3), 28.1 ($C(CH_3)_3$), 26.2 (CH), 22.4 (CH), 22.4 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3248, 2986, 2867, 1693, 1526, 1287, 1245, 1163, 1021, 774, 681. **MS (ESI) m/z calcd. ($C_{18}H_{27}NO_4$ + Na^+):** 344.1838, **found:** 344.1819 (M + Na^+).

t-Butyl (1-hydroxy-1-(4-methoxyphenyl)-4-methylhex-2-en-2-yl)carbamate 172j



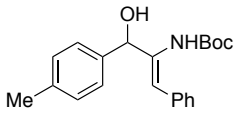
White solid (101 mg, 88% yield); T_m = 90–94 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.28 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.84 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 5.67-5.85 (m, 1H), 5.24-5.26 (m, 1H), 5.19 (d, 1H, *J* = 9.5 Hz, =CH), 5.06 (brs, 1H), 3.77 (s, 3H, OCH_3), 2.22-2.32 (m, 1H), 1.37 (s, 9H, CCH_3), 0.99 (dd, 3H, *J* = 8.0, 6.5 Hz, CH), 0.87 (td, 3H, J = 7.5, 2.0 Hz, CH). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.6 (C_{Ar}), 155.0 (HNCOO), 134.8 (C_{Ar}), 134.0 (C_{Ar}H), 127.3 (C_{Ar}H), 127.2, 113.4, 80.4 (=CH), 75.9 (OCH), 55.1 (OCH_3), 33.1, 29.7, 28.1 ($C(CH_3)_3$), 20.0, 11.9. **IR (neat, ν_{max}, cm^{-1}):** 3257, 2965, 2926, 1693, 1509, 1289, 1245, 1162, 1020, 806, 772, 684. **MS (ESI) m/z calcd. ($C_{19}H_{29}NO_4$ + Na^+):** 358.1994, **found:** 358.1976 (M + Na^+).

t-Butyl (1-cyclohexyl-3-hydroxy-3-(4-methoxyphenyl)prop-1-en-2-yl)carbamate 172k



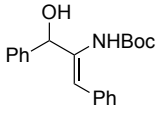
White solid (72 mg, 76% yield); T_m = 129–131 °C. **^{1}H NMR (CDCl$_3$, 400 MHz)**: δ 7.26 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.83 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 5.67 (brs, 1H), 5.20-5.23 (m, 2H), 4.83 (brs, 1H), 3.78 (s, 3H, OCH_3), 2.12-2.17 (m, 1H), 1.63-1.72 (m, 5H), 1.37 (s, 9H, CCH_3), 1.05-1.26 (m, 5H). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 158.8 (C_{Ar}), 155.0 (HNCOO), 134.1 (C_{Ar}), 134.1 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 113.5, 80.6 (=CH), 76.0 (OCH_3), 55.3 (C), 36.0, 32.6, 32.5 , 28.2 ($C(CH_3)_3$), 26.0 (CH), 25.8 (OCH_3), 25.8 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3249, 2981, 2925, 2847, 1694, 1527, 1509, 1286, 1243, 1160, 1021, 870, 685. **MS (ESI) m/z calcd. ($C_{21}H_{31}NO_4$ + H$^+$):** 362.2331, **found:** 362.2311 (M + H$^+$).

t-Butyl (3-hydroxy-1-phenyl-3-(*p*-tolyl)prop-1-en-2-yl)carbamate 172l



White solid (136 mg, 89% yield); T_m = 110–115 °C. **^{1}H NMR (CDCl$_3$, 400 MHz):** ∂ 7.33-7.37 (m, 6H, H_{Ar}), 7.23-7.25 (m, 1H, H_{Ar}), 7.14 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.23 (brs, 1H), 6.11 (brs, 1H), 5.52 (d, 1H, *J* = 7.0 Hz), 2.34 (s, 3H), 1.34 (brs, 9H, CCH_3). **^{13}C NMR (CDCl$_3$, 125 MHz):** ∂ 154.3 (HNCOO), 138.4 (C_{Ar}), 137.0 (C_{Ar}), 135.3 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 81.3, 75.9, 28.2 ($C(CH_3)_3$), 21.3 ($C_{Ar}Me$). **IR (neat, ν_{max}, cm^{-1}):** 3345, 3265, 2992, 1702, 1648, 1555, 1295, 1249, 1158, 1010, 781, 651. **MS (ESI) m/z calcd. ($C_{21}H_{25}NO_3$ + Na$^+$):** 362.1732, **found:** 362.1739 (M + Na$^+$).

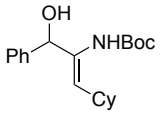
t-Butyl (3-hydroxy-1,3-diphenylprop-1-en-2-yl)carbamate 172m



White solid (190 mg, 85% yield); T_m = 106–110 °C. **^{1}H NMR (CDCl$_3$, 400 MHz)**: δ 7.60-7.58 (m, 2H, H_{Ar}), 7.48-7.44 (m, 5H, H_{Ar}), 7.40-7.34 (m, 2H, H_{Ar}), 6.54 (brs, 1H, NH), 6.31 (s, 1H, C=CH), 5.43-5.80 (m, 2H), 1.45 (brs, 9H, CCH_3). **^{13}C NMR (CDCl$_3$, 100 MHz):** δ 154.1 (HNCOO), 141.2 (C_{Ar}), 128.6

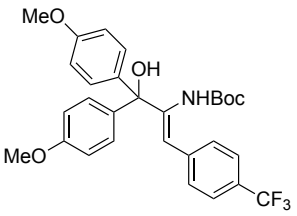
($C_{Ar}H$), 128.5 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.3 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 118.8 (C=CH), 81.0 (C), 75.8 (OCH), 27.9 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3335, 3239, 2986, 1694, 1642, 1523, 1274, 1252, 1163, 1022, 773, 679. **MS (ESI) m/z calcd. ($C_{20}H_{23}NO_3 + Na^+$):** 348.1576, **found:** 348.1573 ($M + Na^+$).

t-Butyl (1-cyclohexyl-3-hydroxy-3-phenylprop-1-en-2-yl)carbamate 172n



White solid (151 mg, 89% yield); T_m = 146–150 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.34–7.36 (m, 2H, H_{Ar}), 7.27–7.31 (m, 2H, H_{Ar}), 7.20–7.23 (m, 1H, H_{Ar}), 5.69 (brs, 1H, NH), 5.22–5.27 (m, 2H), 5.05 (brs, 1H, OH), 2.13–2.20 (m, 1H, CH), 1.63-1.73 (m, 5H, CH), 1.35 (brs, 9H, CCH_3), 1.06–1.30 (m, 5H, CH). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 155.0 (HNCOO), 141.8 (C_{Ar}), 133.9 (C_{Ar}), 128.0 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 126.1 ($C_{Ar}H$), 80.7 (=CH)), 76.5 (OCH), 35.9 (CH), 32.6 (CH), 32.4 (CH), 28.1 ($C(CH_3)_3$), 26.0 (CH), 25.8 (CH), 25.7 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3256, 2925, 2849, 1694, 1526, 1447, 1288, 1164, 1010, 891, 694. **MS (ESI) m/z calcd. ($C_{20}H_{29}NO_3 + Na^+$):** 354.2045, **found:** 354.2043 ($M + Na^+$).

t-Butyl (3-hydroxy-3,3-bis(4-methoxyphenyl)-1-(4-(trifluoromethyl)phenyl)prop-1-en-2-yl)carbamate 172o

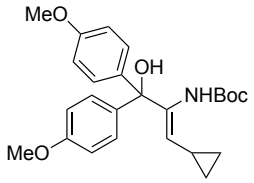


White solid (162 mg, 69% yield); T_m = 114–116 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.52 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.43 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.33 (d, 4H, J = 9.0 Hz, H_{Ar}), 6.86 (d, 4H, J = 9.0 Hz, H_{Ar}), 6.24 (brs, 1H), 5.88 (brs, 1H), 3.80 (s, 6H, OCH_3), 1.18 (brs, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 159.1 (C_{Ar}), 152.7 (HNCOO), 140.1 (C_{Ar}), 136.4 (C_{Ar}), 129.0 (C), 128.5 ($C_{Ar}H$), 127.1 ($C_{Ar}H$), 126.4 (q, J = 270.5 Hz), 125.2 ($C_{Ar}H$), 121.2 ($C_{Ar}H$), 113.5 (=CH), 82.1 (C), 80.9 (C), 55.5 (OCH_3), 27.9 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3255, 3003, 2837, 1677, 1608, 1509, 1458, 1321,

1247, 1161, 1122, 1108, 1065, 828. **MS (ESI) m/z calcd. ($C_{29}H_{30}F_3NO_5$ + Na^+):** 552.1974, **found:** 552.1959 (M + Na^+).

t-Butyl (1-cyclopropyl-3-hydroxy-3,3-bis(4-methoxyphenyl)prop-1-en-2-yl)carbamate

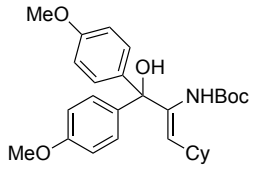
172p



White solid (81 mg, 61% yield); T_m = 140–142 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.20 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 6.74 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 5.84 (brs, 1H), 4.35 (d, 1H, *J* = 9.0 Hz, =CH), 3.70 (s, 6H, OCH_3), 1.37-1.46 (m, 1H, CH), 1.27 (s, 9H, CCH_3), 0.67-0.71 (m, 2H, CH), 0.19-0.23 (m, 2H, CH). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.7 ($C_{Ar}H$), 154.6 (HNCOO), 137.1 (C_{Ar}), 136.6 (C), 131.9 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 113.2 (=CH), 81.6 (C), 80.2 (C), 55.3 (OCH_3), 28.2 ($C(CH_3)_3$), 10.3 (CH_2), 7.1 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3300, 3002, 2963, 2908, 2833, 1685, 1609, 1508, 1284, 1245, 1170, 1035, 826, 812. **MS (ESI) m/z calcd. ($C_{25}H_{31}NO_5$ + Na^+):** 448.2081, **found:** 448.2100 (M + Na^+).

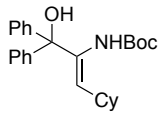
t-Butyl (1-cyclohexyl-3-hydroxy-3,3-bis(4-methoxyphenyl)prop-1-en-2-yl)carbamate

172q



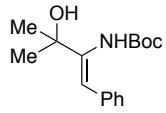
White solid (147 mg, 92% yield); T_m = 144–148 °C. **^{1}H NMR ($CDCl_3$, 400 MHz)**: δ 7.79 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 7.33 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 6.25 (brs, 1H), 5.45 (d, 1H, *J* = 9.0 Hz, =CH), 5.01 (brs, 1H), 4.28 (s, 6H, OCH_3), 2.71-2.79 (m, 1H, CH), 2.16-2.23 (m, 5H, CH), 1.87 (s, 9H, CCH_3), 1,61-1.78 (m, 3H, CH), 1.44-1.53 (m, 2H, CH). **^{13}C NMR ($CDCl_3$, 100 MHz):** δ 158.6 (C_{Ar}), 155.1 (HNCOO), 153.2 (C_{Ar}), 150.2 (C), 136.9 ($C_{Ar}H$), 135.4 ($C_{Ar}H$), 134.6 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 113.2 (=CH), 81.8 (C), 80.2 (C), 55.2 (OCH_3), 37.1 (CH), 32.2 (CH), 28.1 ($C(CH_3)_3$), 26.0 (CH), 25.8 (CH). **IR (neat, ν_{max}, cm^{-1}):** 2924, 2847, 1683, 1606, 1528, 1505, 1246, 1167, 1020, 829, 766, 671. **MS (ESI) m/z calcd. ($C_{28}H_{37}NO_5$ + Na^+):** 490.2560, **found:** 490.2569 (M + Na^+).

t-Butyl (1-cyclohexyl-3-hydroxy-3,3-diphenylprop-1-en-2-yl)carbamate 172r



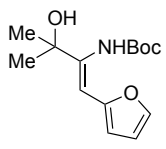
White solid (189 mg, 99% yield). T_m = 139–142 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** ∂ 7.45 (d, 4H, *J* = 7.5 Hz, H_{Ar}), 7.28 (t, 4H, *J* = 7.5 Hz, H_{Ar}), 7.22 (t, 2H, *J* = 7.5 Hz, H_{Ar}), 6.99 (brs, 1h), 5.91 (brs, 1H), 4.84 (d, 1H, *J* = 9.5 Hz, =CH), 2.36 (dtt, 1H, J = 21.0, 11.0, 3.5 Hz, CH), 1.71-1.74 (m, 2H), 1.58-1.65 (m, 3H), 1.30 (s, 9H, CCH_3), 1.21-1.26 (m, 2H, CH), 1.08-1.16 (m, 1H, CH), 0.86-0.94 (m, 2H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 146.7 (HNCOO), 137.4 (C_{Ar}), 135.1 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 127.7 ($C_{Ar}H$), 83.1 (=CH), 80.0 (C), 37.9 (CH), 33.1 (CH), 28.5 ($C(CH_3)_3$), 26.8 (CH), 26.7 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3259, 2928, 2855, 1691, 1522, 1454, 1279, 1178, 1016, 887, 689. **MS (ESI) m/z calcd. ($C_{26}H_{33}NO_3$ + Na^+):** 430.2358, **found:** 430.2362 (M + Na^+).

t-Butyl (3-hydroxy-3-methyl-1-phenylbut-1-en-2-yl)carbamate 172s



White solid (108 mg, 68% yield). T_m = 86–88 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** ∂ 7.43 (d, 2H, *J* = 7.5 Hz, H_{Ar}), 7.27 (t, 2H, *J* = 7.5, H_{Ar}), 7.16 (t, 1H, *J* = 7.5, H_{Ar}), 6.47 (d, 1H, *J* = 3.0 Hz), 4.15 (brs, 1H), 1.41 (s, 6H, CCH_3), 1.30 (brs, 9H, CCH_3). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 154.4 (HNCOO), 129.4 (C), 128.9 (C_{Ar}), 127.4 ($C_{Ar}H$), 120.2 ($C_{Ar}H$), 79.5 (C), 73.1 (C), 28.9 (CCH_3), 28.9 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3520, 3351, 2921, 28102, 1752, 1479, 1023, 902, 699. **MS (ESI) m/z calcd. ($C_{16}H_{23}NO_3$ + Na^+):** 300.1576, **found:** 300.1580 (M + Na^+).

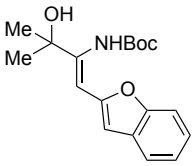
t-Butyl (1-(furan-2-yl)-3-hydroxy-3-methylbut-1-en-2-yl)carbamate 172t



White solid (114 mg, 61% yield). T_m = 92–95 °C. **^{1}H NMR ($CDCl_3$, 400 MHz):** ∂ 7.47 (m, 1H), 7.03 (brs, 1H), 6.43 (m, H), 6.40 (m, 1H), 6.39 (m, 1H), 4.31 (brs, 1H), 1.41 (brs, 9H, CCH_3), 1.39 (s, 6H, CCH_3). **^{13}C NMR**

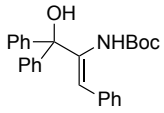
(CDCl$_3$, 125 MHz): ∂ 154.7 (C_{Het}), 152.7 (HNCOO), 142.2 (C), 140.5 ($C_{HetAr}H$), 112.1 ($C_{HetAr}H$), 110.3 ($C_{HetAr}H$), 109.7, 79.7 (=CH), 72.9 (C), 28.8 (C), 28.5 ($C(CH_3)_3$). **IR (neat, ν_{max}, cm^{-1}):** 3509, 3390, 2909, 2810, 1732, 1501, 1438, 1125, 1039, 846, 755. **MS (ESI) m/z calcd. ($C_{14}H_{21}NO_4$ + Na$^+$):** 290.3148, **found:** 290.3160 (M + Na$^+$).

t-Butyl (1-(benzofuran-2-yl)-3-hydroxy-3-methylbut-1-en-2-yl)carbamate 172u



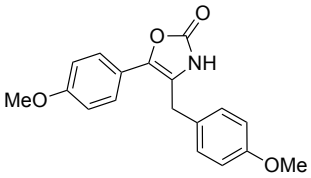
White solid (92 mg, 69% yield). T_m = 98–101 °C. **^{1}H NMR (CDCl$_3$, 400 MHz):** ∂ 7.50 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.41 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.24 (t, 1H, *J* = 8.0 Hz, H_{Ar}), 7.18 (t, 1H, *J* = 8.0 Hz, H_{Ar}), 6.76 (s, 1H, H_{HetAr}), 6.53 (s, 1H, H_{HetAr}), 6.52 (s, 1H, H_{HetAr}), 4.36 (brs, 1H), 1.44 (s, 6H, CCH_3), 1.40 (s, 9H, CCH_3). **^{13}C NMR (CDCl$_3$, 125 MHz):** ∂ 154.3 (C_{HetAr}), 154.2 (C_{HetAr}), 153.2 (HNCOO), 143.3 (C), 129.0 (C_{HetAr}), 123.9 ($C_{Ar}H$), 122.7 ($C_{Ar}H$), 120.6 ($C_{Ar}H$), 110.6 ($C_{HetAr}H$), 108.0 (=CH), 105.0 (C_{HetAr}), 78.9 (C), 72.1 (C), 27.9 ($C(CH_3)_3$), 27.6 (CCH_3). **IR (neat, ν_{max}, cm^{-1}):** 3496, 3390, 2899, 2842, 1722, 1515, 1440, 1158, 1028, 824, 730. **MS (ESI) m/z calcd. ($C_{18}H_{23}NO_4$ + Na$^+$):** 340.1525, **found:** 340.1533 (M + Na$^+$).

t–Butyl (3-hydroxy-1,3,3-triphenylprop-1-en-2-yl)carbamate 172v



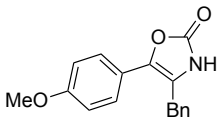
White solid (125 mg, 78% yield). T_m = 132–136 °C. **^{1}H NMR (CDCl$_3$, 400 MHz):** ∂ 7.75–7.82 (m, 2H, H_{Ar}), 7.65 (t, 2H, *J* = 8.5 Hz, H_{Ar}), 7.30–7.51, (m, 11H, H_{Ar}), 6.29 (brs, 1H), 5.69 (s, 1H, =CH), 5.16 (brs, 1H), 1.75 (s, 9H, CCH_3). **^{13}C NMR (CDCl$_3$, 125 MHz):** ∂. **IR (neat, ν_{max}, cm^{-1}):** 3301, 2915, 2867, 1709, 1525, 1241, 1169, 1025, 899, 711. **MS (ESI) m/z calcd. ($C_{26}H_{27}NO_3$ + Na$^+$):** 424.1889, **found:** 424.1895 (M + Na$^+$).

4-(4-Methoxybenzyl)-5-(4-methoxyphenyl)oxazol-2(3*H*)-one 174a



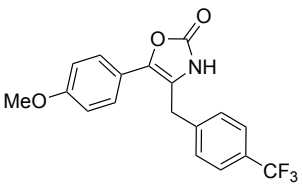
White solid (19 mg, 59% yield). T_m = 90–94 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.47 (s, 1H, NH), 7.47 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.22 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.99 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.89 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 3.94 (s, 2H, CH), 3.82 (s, 3H, CH), 3.77 (s, 3H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 160.3 (C_{Ar}), 159.8 (C_{Ar}), 155.3 (C), 130.1 (C_{Ar}), 129.8 ($C_{Ar}H$), 127.3 (C_{Ar}), 125.3 ($C_{Ar}H$), 122.2 (C), 120.4 (C), 115.3 ($C_{Ar}H$), 115.1 ($C_{Ar}H$), 55.7 (CH_3), 55.2 (CH_3), 30.8 (CH_2). **IR (neat, ν_{max}, cm^{-1}):** 3183, 2950, 1735, 1608, 1515, 1241. **MS (ESI) m/z calcd. ($C_{18}H_{17}NO_4$ + Na$^+$):** 334.1052, **found:** 334.1055 (M + Na$^+$).

4-Benzyl-5-(4-methoxyphenyl)oxazol-2(3*H*)-one 174b



White solid (17.5 mg, 62% yield). T_m = 88–94 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.33 (brs, 1H, NH), 7.43 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.30-7.34 (m, 2H), 7.23-7.26 (m, 3H), 6.99 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 3.93 (s, 2H, CH), 3.82 (s, 3H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 159.51 (C_{Ar}), 156.3 (C), 136.2 (C_{Ar}), 136.1 (C_{Ar}), 129.2 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 127.4 ($C_{}$), 126.8 ($C_{Ar}H$), 120.7 (C_{Ar}), 118.83 (C), 114.4 ($C_{Ar}H$), 55.5 (CH), 30.5 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3187, 2955, 1740, 1604, 1510, 1246. **MS (ESI) m/z calcd. ($C_{17}H_{15}NO_3$ + Na$^+$):** 304.0950, **found:** 304.0942 (M + Na$^+$).

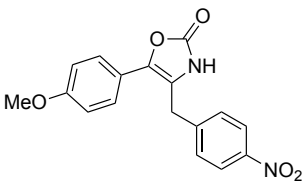
5-(4-Methoxyphenyl)-4-(4-(trifluoromethyl)benzyl)oxazol-2(3*H*)-one 174c



White solid (34 mg, 98% yield). T_m = 88–90 °C**. ^{1}H NMR (CDCl$_3$, 400 MHz):** ∂ 8.31 (brs, 1H, NH), 7.61 (d, 2H *J* = 8.0 Hz, H_{Ar}), 7.42 (d, 2H, *J* = 9.0 Hz) , H_{Ar}, 7.38 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 6.94 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 4.01 (s, 2H, CH), 3.84 (s, 3H, CH). **^{13}C**

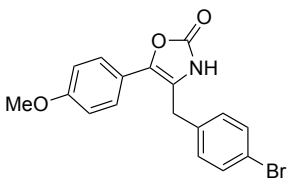
NMR ($CDCl_3$, 125 MHz): ∂ 159.8 (C_{Ar}), 155.6 (C), 140.0 (C_{Ar}), 136.9 (C_{Ar}), 128.8 ($C_{Ar}H$), 128.67 (q, J = 237.0 Hz, $C_{Ar}H$), 126.9 (C), 126.3 (q, J = 4.0 Hz, C), 120.3 (C), 117.2 ($C_{Ar}H$), 114.6 ($C_{Ar}H$), 55.5 (CH_3), 30.4 (CH_2). **^{19}F NMR ($CDCl_3$, 470 MHz):** ∂ -62.59. **IR (neat, ν_{max}, cm^{-1}):** 3178, 2927, 1741, 1611, 1513, 1252. **MS (ESI) m/z calcd. ($C_{18}H_{14}F_3NO_3 + Na^+$):** 372.0823, **found:** 372.0819 ($M + Na^+$).

5-(4-Methoxyphenyl)-4-(4-nitrobenzyl)oxazol-2(3*H*)-one **174d**



Whites solid (20 mg, 60% yield). T_m = 118–123 °C. **^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.83 (s, 1H, NH), 8.20 (d, 2H, J = 8.5 Hz, H_{Ar}), 7.54 (d, 2H, J = 8.5 Hz) , H_{Ar}, 7.38 (d, 2H, J = 9.0 Hz, H_{Ar}), 6.98 (d, 2H, J = 9.0 Hz, H_{Ar}), 4.08 (s, 2H, CH_2), 3.76 (s, 3H, CH). **^{13}C NMR (d6-DMSO, 125 MHz):** ∂ 158.8 (C_{Ar}), 154.2 (C_{Ar}), 146.5 (C), 145.1 (C_{Ar}), 134.8 (C), 129.3 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 123.8 ($C_{Ar}H$), 120.3 (C_{Ar}), 117.8 (C), 114.5 ($C_{Ar}H$), 55.2 (CH), 29.3 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3174, 2961, 1733, 1607, 1511, 1251. **MS (ESI) m/z calcd. ($C_{17}H_{14}N_2O_5 + Na^+$):** 349.0800, **found:** 349.0781 ($M + Na^+$).

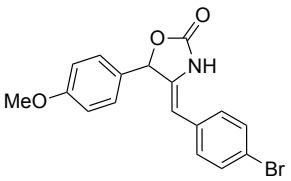
4-(4-Bromobenzyl)-5-(4-methoxyphenyl)oxazol-2(3*H*)-one **174e**



Colourless oil (17 mg, 47% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** ∂ 8.47 (brs, 1H, NH), 7.47 (d, 2H, J = 8.5 Hz, H_{Ar}), 7.42 (d, 2H, J = 9.0 Hz, H_{Ar}), 7.12 (d, 2H, J = 8.5 Hz, H_{Ar}), 6.94 (d, 2H, J = 9.0 Hz, H_{Ar}), 3.89 (s, 2H, CH), 3.83 (s, 3H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 160.9 (C_{Ar}), 156.0 (C_{Ar}), 151.3 (C), 141.4 (C_{Ar}), 135.5 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 114.5 (C), 111.7 (C_{Ar}), 106.7 (C), 90.2 ($C_{Ar}H$), 82.2 (CH), 55.5 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3180, 2963, 1757, 1609, 1487, 1251. **MS (ESI) m/z calcd.**

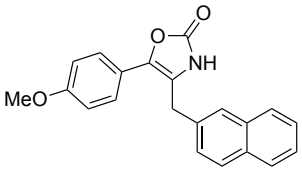
($C_{17}H_{14}BrNO_3 + Na^+$): 382.0055 & 384.0044, **found:** 382.0050 & 384.0031 (M + Na^+).

4-(4-Bromobenzylidene)-5-(4-methoxyphenyl)oxazolidin-2-one 175e′



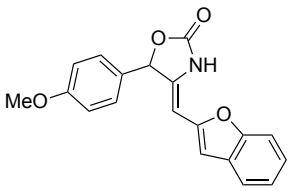
Colourless oil (7.5 mg, 21% yield). **^{1}H NMR ($CDCl_3$, 500 MHz):** ∂ 7.88 (brs, 1H, NH), 7.46 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.36 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.05 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.96 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.06 (d, 1H, *J* = 1.5 Hz, =CH), 5.18 (d, 1H, *J* = 1.5 Hz, CH), 3.84 (s, 3H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 160.9 (C_{Ar}), 156.7 (C_{Ar}), 137.2 (C), 134.0 (C_{Ar}), 132.3 ($C_{Ar}H$), 129.4 ($C_{Ar}H$), 128.7 ($C_{Ar}H$), 128.5 (C), 120.5 (C), 114.6 (=CH), 100.0 (CH), 82.9 (CH), 55.5 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3255, 2960, 1760, 1611, 1514, 1248. **MS (ESI) m/z calcd. ($C_{17}H_{14}BrNO_3 + Na^+$):** 382.0055 & 384.0044, **found:** 382.0050 & 384.0031 (M + Na^+).

5-(4-Methoxyphenyl)-4-(naphthalen-2-ylmethyl)oxazol-2(3*H*)-one 174f



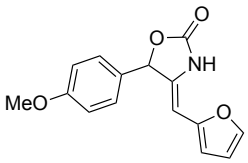
Yellow solid (33 mg, 99% yield). T_m = 120–124 °C**. ^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.87 (s, 1H, NH), 7.87-7.90 (m, 3H, H_{Ar}), 7.76 (s, 1H, H_{Ar}), 7.47-7.50 (m, 2H, H_{Ar}), 7.42 (d, 2H, H_{Ar}), 6.98 (d, 2H, H_{Ar}), 4.09 (s, 2H, CH), 3.75 (s, 3H, CH). **^{13}C NMR (d6-DMSO, 125 MHz):** ∂ 158.7 (C_{Ar}), 154.5 (C), 134.7 (C_{Ar}), 133.1 (C_{Ar}), 131.9 (C_{Ar}), 128.3 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 126.0 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 120.7 (C), 119.0 (C_{Ar}), 114.5 (C), 55.1 (CH), 29.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3188, 2960, 1738, 1609, 1509, 1248. **MS (ESI) m/z calcd. ($C_{21}H_{17}NO_3 + Na^+$):** 354.1106, **found:** 354.1098 (M + Na^+).

4-(Benzofuran-2-ylmethylene)-5-(4-methoxyphenyl)oxazolidin-2-one **174g**



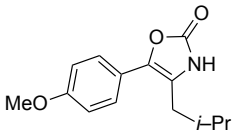
Brown solid (22 mg, 68% yield). T_m = 108–112 °C. **^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.84 (s, 1H, NH), 7.55 (dd, 1H, *J* = 8.0, 1.0 Hz, H_{Ar}), 7.49 (dd, 1H, *J* = 8.0, 1.0 Hz, H_{Ar}), 7.38 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.22 (td, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 7.17 (td, 1H, *J* = 7.5, 1.5 Hz, H_{Ar}), 7.01 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.69 (s, 1H, H_{HetAr}), 6.30 (d, 1H, *J* = 2.0 Hz, =CH), 5.21 (d, 1H, *J* = 2.0 Hz, CH), 3.78 (s, 3H, CH_3). **^{13}C NMR (d6-DMSO, 125 MHz):** ∂ 160.1 (C_{Ar}), 156.5 (C), 153.8 (C_{Ar}), 152.8 (C_{Ar}), 140.2 (C_{Ar}), 129.3 ($C_{Ar}H$), 129.0 (C), 128.8 ($C_{Ar}H$), 123.5 ($C_{Ar}H$), 122.9 ($C_{Ar}H$), 114.4 ($C_{Ar}H$), 111.2 ($C_{Ar}H$), 101.6 ($C_{Ar}H$), 88.5 (=CH), 80.6 (CH), 55.3 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3281, 2961, 1766, 1611, 1514, 1248. **MS (ESI) m/z calcd. ($C_{15}H_{13}NO_4$ + Na$^+$):** 294.0742, **found:** 294.0739 (M + Na$^+$).

4-(Furan-2-ylmethylene)-5-(4-methoxyphenyl)oxazolidin-2-one **174h**



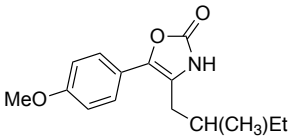
Yellow oil (14 mg, 51% yield). **^{1}H NMR ($CDCl_3$, 500 MHz):** ∂ 8.23 (brs, 1H, NH), 7.41 (m, 1H, H_{Ar}), 7.34 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.94 (d, 2H, *J* = 8.5 Hz), 6.38 (dd, 1H, *J* = 3.0, 2.0 Hz, =CH), 6.06 (d, 1H, *J* = 1.5 Hz, H_{HetAr}), 6.03 (d, 1H, *J* = 3.0 Hz, CH), 5.11 (d, 1H, *J* = 1.5 Hz, CH), 3.83 (s, 3H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 160.9 (C_{Ar}), 156.0 (C), 151.3 (C_{Ar}), 141.4 ($C_{Ar}H$), 135.5 (C_{Ar}), 129.3 ($C_{Ar}H$), 128.4 (C), 114.5 ($C_{Ar}H$), 111.7 ($C_{Ar}H$), 106.7 ($C_{Ar}H$), 90.2 (=CH), 82.2 (CH), 55.5 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3281, 2961, 1766, 1611, 1514, 1248. **MS (ESI) m/z calcd. ($C_{15}H_{13}NO_4$ + Na$^+$):** 294.0742, **found:** 294.0739 (M + Na$^+$).

4-Isobutyl-5-(4-methoxyphenyl)oxazol-2(3*H*)-one 174i



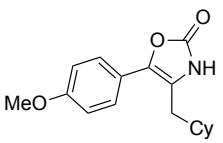
White solid (19 mg, 94% yield). T_m = 126–128 °C**. ^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.687 (s, 1H, NH), 7.37 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.98 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 3.76 (s, 3H, CH), 2.39 (d, 2H, *J* = 7.0 Hz, CH), 1.93 (hept, 1H, *J* = 7.0 Hz, CH), 0.90 (d, 6H, *J* = 7.0 Hz, CH). **^{13}C NMR (d6-DMSO, 125 MHz):** ∂ 158.4 (C_{Ar}), 154.5 (C), 133.9 (C_{Ar}), 126.0 (C_{Ar}H), 121.06 (C), 120.3 (C), 114.4 (C_{Ar}H), 55.2 (CH), 32.5 (CH), 27.1 (CH), 22.0 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3184, 2958, 1744, 1605, 1512, 1249. **MS (ESI) m/z calcd. ($C_{14}H_{17}NO_3$ + Na$^+$):** 270.1106, **found:** 270.1101 (M + Na$^+$).

5-(4-Methoxyphenyl)-4-(2-methylbutylidene)oxazolidin-2-one 174j



White solid (22.5 mg, 86% yield). T_m = 90–94 °C**. ^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.65 (s, 1H, NH), 7.35 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 6.96 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 3.74 (s, 3H, CH), 2.48 (dd, 1H, *J* = 14.5, 6.5 Hz, CH), 2.30 (dd, 1H, *J* = 14.5, 6.5 Hz, CH), 1.69 (oct, 1H, *J* = 7.5 Hz, CH), 1.39-1.29 (m, 1H, CH), 1.18-1.07 (m, 1H, CH), 0.84-0.80 (m, 6H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** ∂ 158.4 (C_{Ar}), 154.5 (C), 133.9 (C_{Ar}), 126.0 (C_{Ar}H), 121.1 (C), 120.3 (C), 114.3 (C_{Ar}H), 55.1 (CH), 33.2 (CH), 30.7 (CH), 28.6 (CH), 18.6 (CH), 11.1 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3203, 2960, 1741, 1603, 1513, 1251. **MS (ESI) m/z calcd. ($C_{15}H_{19}NO_3$ + Na$^+$):** 284.1263, **found:** 284.1257 (M + Na$^+$).

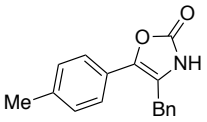
4-(Cyclohexylmethyl)-5-(4-methoxyphenyl)oxazol-2(3H)-one 174k

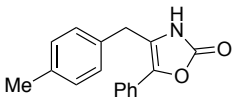


White solid (28 mg, 97% yield). T_m = 129–131 °C**. ^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.64 (s, 1H, CH), 7.37 (d, 2H, *J* = 9.0 Hz, , H_{Ar}), 6.98 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 3.77 (s, 3H, CH), 2.40 (d, 2H, *J* = 7.5 Hz, CH), 1.67-1.57 (m, 6H, CH), 1.22-.1.08 (m, 3H, CH), 0.98-0.90 (m, 2H, CH). **^{13}C NMR**

(d6-DMSO, 125 MHz): ∂ 158.4 (C_{Ar}), 154.4 (C), 133.9 (C_{Ar}), 125.9 ($C_{Ar}H$), 121.1 (C), 119.9 (C), 114.3 ($C_{Ar}H$), 55.1 (CH), 36.4 (CH), 32.4 (CH), 31.1 (CH), 25.8 (CH), 25.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3183, 2921, 1744, 1607, 1513, 1251. **MS (ESI) m/z calcd. ($C_{17}H_{21}NO_3 + Na^+$):** 310.1419, **found:** 310.1414 ($M + Na^+$).

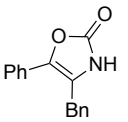
4-Benzyl-5-(*p*-tolyl)oxazol-2(3*H*)-one **174l** and 4-(4-Methylbenzyl)-5-phenyloxazol-2(3*H*)-one **174l′**





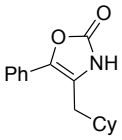
White solid (17 mg, 65%. Ratio = 10:1). T_m = 92–96 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.56-9.60 (m, 2H, NH), 7.55 (d, 2H, H_{Ar}) 7.43 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.30-7.35 (m, 4H, H_{Ar}), 7.24 (d, 2H, *J* = 8.0 Hz, H_{Ar}), 7.16 (d, 2H, H_{Ar}), 7.14 (d, 2H, H_{Ar}), 4.05 (s, 2H, CH), 4.02 (s, 2H, CH), 2.35 (s, 3H, CH), 2.29 (s, 3H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 155.3 (C), 138.4 (C_{Ar}), 138.0, 137.3, 136.2, 130.4, 129.7, 129.1, 127.8, 126.9, 125.6, 121.0 (C), 30.8 (CH), 21.3 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3180, 2951, 1742, 1603, 1514, 1245. **MS (ESI) m/z calcd. ($C_{17}H_{15}NO_2 + Na^+$):** 288.1000, **found:** 288.0982 ($M + Na^+$).

4-Benzyl-5-phenyloxazol-2(3*H*)-one **174m**[9]



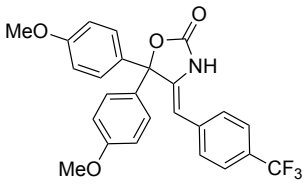
White solid (10.5 mg, 42% yield). T_m = 106–110 °C**. ^{1}H NMR ($CDCl_3$, 400 MHz):** ∂ 9.05 (brs, 1H, NH), 7.45 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.18–7.35 (m, 8H, H_{Ar}), 3.91 (s, 2H, CH_2). **^{13}C NMR ($CDCl_3$, 125 MHz):** 156.0 (C), 136.1 (C_{Ar}), 135.8 (C_{Ar}), 129.3 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 128.1 (C), 127.6 ($C_{Ar}H$), 125.1 ($C_{Ar}H$), 120.3 (C), 30.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3275, 2950, 1759, 1581, 1499, 1229. **MS (ESI) m/z calcd. ($C_{16}H_{13}NO_2 + Na^+$):** 274.0844, **found:** 274.0833 ($M + Na^+$).

4-(Cyclohexylmethyl)-5-phenyloxazol-2(3*H*)-one 174n



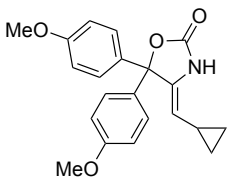
White solid (15 mg, 58% yield). T_m = 146–150 °C. **^{1}H NMR (d6-DMSO, 400 MHz):** ∂ 10.78 (s, 1H, NH), 7.39-7.46 (m, 4H, H_{Ar}), 7.25-7.29 (m, 1H, H_{Ar}), 2.46 (d, 2H, *J* = 7.0 Hz, CH), 1.58-1.68 (m, 6H, CH), 1.09-1.22 (m, 3H, CH), 0.92-1.00 (m, 2H, CH). **^{13}C NMR (d6-DMSO, 125 MHz):** ∂ 154.3 (C), 133.7 (C_{Ar}), 128.9 ($C_{Ar}H$), 128.5 (C), 127.0 (C), 124.1 ($C_{Ar}H$), 121.9 ($C_{Ar}H$), 36.4 (CH), 32.3 (CH), 31.2 (CH), 25.8 (CH), 25.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3192, 2942, 1744, 1600, 1515, 1233. **MS (ESI) m/z calcd. ($C_{16}H_{19}NO_2$ + Na^+):** 280.1313, **found:** 280.1319 (M + Na^+).

5,5-Bis(4-methoxyphenyl)-4-(4-(trifluoromethyl)benzylidene)oxazolidin-2-one 175o



White solid (32 mg, 70% yield). T_m = 114–116 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.70 (brs, 1H, NH), 7.64 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.60 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.39 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 6.99 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 5.55 (s, 1H, =CH), 3.83 (s, 6H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 161.1 (C_{Ar}), 155.9 (C), 143.6 (C_{Ar}), 140.4 (C_{Ar}), 133.9 (C), 129.8 ($C_{Ar}H$), 129.1 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 126.4 (q, C_{Ar}), 114.7 ($C_{Ar}H$), 102.5 (=CH), 55.8 (CH). **^{19}F NMR (d6-acetone, 470 MHz):** ∂ –62.92. **IR (neat, ν_{max}, cm^{-1}):** 3253, 2969, 2838, 1760, 1611, 1583, 1510, 1323, 831. **MS (ESI) m/z calcd. ($C_{25}H_{20}F_3NO_4$ + H^+):** 456.1423, **found:** 456.1417 (M + H^+).

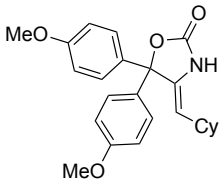
4-(Cyclopropylmethylene)-5,5-bis(4-methoxyphenyl)oxazolidin-2-one 175p



White solid (35 mg, 99% yield). T_m = 140–142 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 8.70 (brs, 1H, NH), 7.18 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 7.14 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.91 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 6.87 (d, 2H, *J* = 8.5 Hz, H_{Ar}), 5.06 (d, 1H, J = 7.5 Hz, =CH), 3.80 (s, 3H, CH), 3.78 (s,

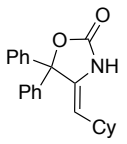
3H, CH), 0.95-1.02 (m, 1H, CH), 0.34-0.40 (m, 1H, CH), 0.24-0.29 (m, 1H, CH), 0.16-0.21 (m, 1H, CH), -0.30–0.25 (m, 1H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 159.8 (C_{Ar}), 159.5 (C_{Ar}), 157.2 (C), 135.3 (C_{Ar}), 133.9 (C_{Ar}), 133.6 (C_{Ar}), 132.0 ($C_{Ar}H$), 131.1 ($C_{Ar}H$), 115.0 ($C_{Ar}H$), 113.5 (C), 82.6 (=CH), 55.6 (CH), 15.2 (CH), 3.4 (CH_2), 1.7 (CH_2). **IR (neat, ν_{max}, cm^{-1}):** 3256, 3004, 2954, 2837, 1753, 1665, 1508, 1282, 1027. **MS (ESI) m/z calcd. ($C_{21}H_{21}NO_4$ + Na$^+$):** 374.1368, **found:** 374.1363 (M + Na$^+$).

4-(Cyclohexylmethylene)-5,5-bis(4-methoxyphenyl)oxazolidin-2-one 175q



White solid (39 mg, 99% yield). T_m = 144–148 °C**. ^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.13 (brs, 1H, NH), 7.29 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 6.94 (d, 4H, *J* = 9.0 Hz, H_{Ar}), 4.25 (d, 1H, *J* = 9.5 Hz, =CH), 3.81 (s, 6H, CH), 2.34-2.40 (m, 1H, CH), 1.59-1.71 (m, 5H, CH), 1.25-1.34 (m, 2H, CH), 1.05-1.20 (m, 3H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 160.7 (C_{Ar}), 156.0 (C), 138.9 (C_{Ar}), 134.7 (C_{Ar}), 129.5 ($C_{Ar}H$), 114.3 ($C_{Ar}H$), 109.7 (=CH), 90.4 (C), 55.7 (CH), 36.8 (CH), 34.0 (CH), 26.7 (CH), 26.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3185, 3083, 2912, 1743, 1704, 1510, 1257. **MS (ESI) m/z calcd. ($C_{24}H_{27}NO_4$ + Na$^+$):** 416.1838, **found:** 416.1832 (M + Na$^+$).

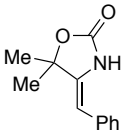
4-(Cyclohexylmethylene)-5,5-diphenyloxazolidin-2-one 175r



White solid (29 mg, 87% yield). T_m = 140–144 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.19 (brs, 1H, NH), 7.37-7.43 (m, 10H, H_{Ar}), 4.34 (d, 1H, *J* = 9.5 Hz, =CH), 2.39 (qt, 1H, *J* = 10 Hz, 3.5 Hz, CH), 1.65-1.72 (m, 4H, CH), 1,26-1.34 (m, 3H, CH), 1.07-1.21 (m, 3H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 155.9 (C), 142.7 (C_{Ar}), 138.2 (C_{Ar}), 135.6 (C), 129.4 ($C_{Ar}H$), 129.3 ($C_{Ar}H$), 128.1 ($C_{Ar}H$), 110.4 (=CH), 90.4 (C), 37.0 (CH), 34.0 (CH), 26.7 (CH), 26.6 (CH). **IR (neat, ν_{max},**

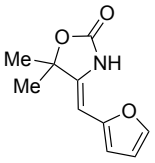
cm^{-1}): 3258, 3081, 1745, 1505, 1201. **MS (ESI) m/z calcd. ($C_{22}H_{23}NO_2$ + Na^+):** 356.1626, **found:** 356.1618 (M + Na^+).

4-Benzylidene-5,5-dimethyloxazolidin-2-one **175s**[10]



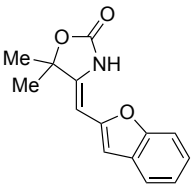
Colourless oil (14 mg, 91% yield). **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.18 (brs, 1H, NH), 7.35 (d, 2H, J = 7.5 Hz, H_{Ar}), 7.31 (t, 2H, J = 7.5 Hz, H_{Ar}), 7.15 (t, 1H, J = 7.5 Hz, H_{Ar}), 5.50 (s, 1H, =CH), 1.60 (s, 6H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 156.3 (C), 143.5 (C_{Ar}), 136.8 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 126.7 (=CH), 97.5 (C), 85.0 (CH), 28.3 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3257, 2985, 1754, 1494, 1193, 1016. **MS (ESI) m/z calcd. ($C_{12}H_{13}NO_2$ + Na^+):** 226.0844, **found:** 226.0838 (M + Na^+).

4-(Furan-2-ylmethylene)-5,5-dimethyloxazolidin-2-one **175t**



Pale yellow oil (9 mg, 47% yield). **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.08 (brs, 1H, NH), 7.49 (d, 1H, *J* = 2.0 Hz, H_{HetAr}), 6.42-6.43 (dd, 1H, *J* = 3.0, 2.0 Hz, H_{HetAr}), 6.21 (d, 1H, *J* = 3.0 Hz, H_{HetAr}), 5.49 (s, 1H, =CH), 1.57 (s, 6H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 155.7 (C), 152.6 (C_{Ar}), 142.7 (C_{Ar}), 142.0 ($C_{Ar}H$), 112.2 ($C_{Ar}H$), 106.5 ($C_{Ar}H$), 87.3 (=CH), 84.6 (C), 28.0 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3269, 2949, 1762, 1691, 1518, 1255. **MS (ESI) m/z calcd. ($C_{14}H_{13}NO_3$ + Na^+):** 216.0637, **found:** 216.0630 (M + Na^+).

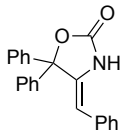
4-(Benzofuran-2-ylmethylene)-5,5-dimethyloxazolidin-2-one **175u**



Colourless oil (12.5 mg, 52% yield). **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.53 (brs, 1H, NH), 7.54 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.51 (d, 1H, *J* = 8.0 Hz, H_{Ar}), 7.17-7.23 (m, 2H, H_{Ar}), 6.59 (s, 1H, H_{HetAr}), 5.65 (s, 1H, =CH), 1.63 (s, 6H, CH_3). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 155.7 (C), 155.4 (C_{Ar}), 155.0 (C_{Ar}), 145.9 (C_{Ar}), 130.1 ($C_{Ar}H$), 124.5 ($C_{Ar}H$), 124.0 ($C_{Ar}H$), 121.2

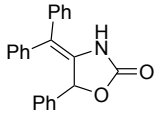
(C_{Ar}), 112.0 ($C_{Ar}H$), 102.6 ($C_{Ar}H$), 86.9 (C_{Ar}), 84.8 (C), 27.9 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3273, 2948, 1760, 1688, 1511, 1249. **MS (ESI) m/z calcd. ($C_{14}H_{13}NO_3$ + Na^+):** 266.0793, **found:** 266.0790 (M + Na^+).

4-Benzylidene-5,5-diphenyloxazolidin-2-one**175v**



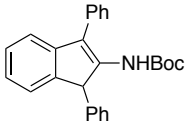
White solid (25 mg, 38% yield). T_m = 129–132 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.21 (brs, 1H, NH), 7.47–7.59 (m, 5H, $_{HAr}$) 7.32–7.41 (m, 10H, H_{Ar}), 5.52 (s, 1H, =CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 154.8 (C), 142.6 (C_{Ar}), 143.1 (C_{Ar}), 138.9 (C_{Ar}), 137.2 ($C_{Ar}H$), 135.9 (C), 128.9 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 127.2 ($C_{Ar}H$), 111.2 (=CH). **IR (neat, ν_{max}, cm^{-1}):** 3265, 3092, 1741, 1498, 1190, 945, 759. **MS (ESI) m/z calcd. ($C_{22}H_{17}NO_2$ + Na^+):** 350.1157, **found:** 350.1149 (M + Na^+).

4-(Diphenylmethylene)-5-phenyloxazolidin-2-one**175v′**



White solid (18.5 mg, 28% yield). T_m = 125–129 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 9.14 (brs, 1H, NH), 7.56–7.70 (m, 5H, H_{Ar}) 7.39–7.52 (m, 10H, H_{Ar}), 6.81 (s, 1H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 155.6 (C), 143.4 (C_{Ar}), 144.2 (C_{Ar}), 139.8 (C_{Ar}), 137.5 ($C_{Ar}H$), 136.2 (C), 130.0 ($C_{Ar}H$), 129.5 ($C_{Ar}H$), 129.0 ($C_{Ar}H$), 128.5 ($C_{Ar}H$), 127.5 ($C_{Ar}H$), 112.6 (CH). **IR (neat, ν_{max}, cm^{-1}):** 3268, 3089, 1742, 1501, 1195, 947, 756. **MS (ESI) m/z calcd. ($C_{22}H_{17}NO_2$ + Na^+):** 350.1157, **found:** 350.1149 (M + Na^+).

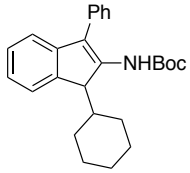
t-Butyl (1-cyclohexyl-3-phenyl-1*H*-inden-2-yl)carbamate **243r**



White solid (13 mg, 19% yield). T_m = 89–93 °C. **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 7.57–7.65 (m, 3H, H_{Ar}), 7.37–7.54 (m, 5H, H_{Ar}), 7.31–7.49 (m, 4H, H_{Ar}), 7.23–7.28 (m, 2H, H_{Ar}), 6.29 (brs, 1H), 3.35 (s, 1H, CH), 1.29 (s, 9H, CCH_3). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 148.9 (C), 140.9 (C_{Ar}), 140.5

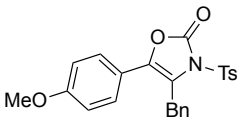
(C_{Ar}), 140.0 (C_{Ar}), 135.2 (C_{Ar}), 129.5 (C_{ArH}), 129.1 (C_{ArH}), 128.8 (C_{ArH}), 128.5 (C_{ArH}), 127.8 (C_{ArH}), 127.4 (C_{ArH}), 127.0 (C_{ArH}), 126.8 (C_{ArH}), 126.5 (C_{ArH}), 119.2 (C), 113.2 (C), 85.9 (C), 46.9 (CH), 29.2 (CH). **IR (neat, ν_{max}, cm^{-1}):** 2962, 2928, 1704, 1611, 1469, 1232, 1162, 1041, 808, 769. **MS (ESI) m/z calcd. ($C_{26}H_{25}NO_2$ + Na^+):** 406.1783, **found:** 406.1771 ($M + Na^+$).

t-Butyl (1,3-diphenyl-1*H*-inden-2-yl)carbamate 243v



Colourless oil (18 mg, 54% yield). **^{1}H NMR (d6-acetone, 500 MHz):** ∂ 7.37–7.54 (m, 5H, H_{Ar}), 7.20–7.35 (m, 3H, H_{Ar}), 7.17 (t, 1H, J = 8.5 Hz, H_{Ar}), 6.98 (brs, 1H), 3.20 (d, 1H, J = 7.0 Hz, CH), 2.30 (dtt, 1H, J = 21.0, 7.0, 3.5 Hz, CH), 1.68–1.71 (m, 2H), 1.55-1.63 (m, 3H), 1.26 (s, 9H, CCH_3), 1.17–1.24 (m, 2H, CH), 1.04–1.11 (m, 1H, CH), 0.80–0.89 (m, 2H, CH). **^{13}C NMR (d6-acetone, 125 MHz):** ∂ 149.7 (C), 141.6 (C_{Ar}), 141.3 (C_{Ar}), 138.8 (C_{Ar}), 130.2 (C_{ArH}), 129.9 (C_{ArH}), 127.9 (C_{ArH}), 127.6 (C_{ArH}), 126.8 (C_{ArH}), 126.1 (C_{ArH}), 117.3 (C), 115.8 (C), 84.1 (C), 47.8 (CH), 32.5 (CH), 31.8 (CH), 28.9 (CH), 27.1 (CH), 26.8 (CH). **IR (neat, ν_{max}, cm^{-1}):** 2951, 2935, 2889, 2765, 1736, 1628, 1441, 1255, 1179, 1067, 911, 819, 721. **MS (ESI) m/z calcd. ($C_{26}H_{31}NO_2$ + Na^+):** 412.2252, **found:** 412.2265 ($M + Na^+$).

4-Benzyl-5-(4-methoxyphenyl)-3-tosyloxazol-2(3*H*)-one *N*–Ts–174b



4-Benzyl-5-(4-methoxyphenyl)oxazol-2(3*H*)-one (281 mg) was dissolved in DMF (2 mL) at 0 ºC, followed by addition of NaH (44 mg, 1.1 eq.). The resulting mixture was stirred at 0 ºC for 1 h. *p*-TsCl (228 mg, 1.2 eq.) was added to the reaction suspension and stirred at RT for 17 h. Upon completion, the reaction was quenched with water (20 mL). The organic layer was separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography (petrol:EtOAc = 6:1) to give the title

compound as white solid (290 mg, 67% yield). **^{1}H NMR ($CDCl_3$, 400 MHz):** ∂ 7.32 (d, 2H, *J* = 9.0 Hz, H_{Ar}), 7.21-7.24 (m, 5H, H_{Ar}), 7.14-7.16 (m, 2H, H_{Ar}), 7.00 (d, 2H, *J* = 8.5 Hz), 6.80 (d, 2H, *J* = 9.0 Hz), 4.21 (s, 2H, CH), 3.69 (s, 3H, CH), 2.26 (s, 3H, CH). **^{13}C NMR ($CDCl_3$, 125 MHz):** δ 160.5 (C_{Ar}), 150.6 (C), 145.9 (C_{Ar}), 137.1 (C_{Ar}), 133.9 (C_{Ar}), 129.5 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 128.6 ($C_{Ar}H$), 128.3 ($C_{Ar}H$), 128.0 ($C_{Ar}H$), 127.0 ($C_{Ar}H$), 119.4 ($C_{Ar}H$), 114.5 (C), 55.4 (CH), 30.0 (CH), 21.7 (CH). **IR (neat, ν_{max}, cm^{-1}):** 2926, 1782, 1671, 1574, 1494, 1300, 1174, 1026, 665, 567, 543. **MS (ESI) m/z calcd. ($C_{24}H_{21}NO_5S + Na^+$):** 458.1038, **found:** 458.1056 ($M + Na^+$). T_m = 112–116 °C.

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Chapter 7

7.0 References

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